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Interventions for impetigo (Review)

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[Intervention Review]

Interventions for impetigo

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ABSTRACT

Background

Impetigo is a common, superficial bacterial skin infection, which is most frequently encountered in children. There is no generally agreed standard therapy, and guidelines for treatment differ widely. Treatment options include many different oral and topical antibiotics as well as disinfectants. This is an updated version of the original review published in 2003.

Objectives

To assess the effects of treatments for impetigo, including non-pharmacological interventions and 'waiting for natural resolution'.

Search methods

We updated our searches of the following databases to July 2010: the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (from 2005), EMBASE (from 2007), and LILACS (from 1982). We also searched online trials registries for ongoing trials, and we handsearched the reference lists of new studies found in the updated search.

Selection criteria

Randomised controlled trials of treatments for non-bullous, bullous, primary, and secondary impetigo.

Data collection and analysis

Two independent authors undertook all steps in data collection. We performed quality assessments and data collection in two separate stages.

Main results

We included 57 trials in the first version of this review. For this update 1 of those trials was excluded and 12 new trials were added. The total number of included trials was, thus, 68, with 5578 participants, reporting on 50 different treatments, including placebo. Most trials were in primary impetigo or did not specify this.

For many of the items that were assessed for risk of bias, most studies did not provide enough information. Fifteen studies reported blinding of participants and outcome assessors.

Topical antibiotic treatment showed better cure rates than placebo (pooled risk ratio (RR) 2. 24, 95% confidence interval (CI) 1.61 to 3.13) in 6 studies with 575 participants. In 4 studies with 440 participants, there was no clear evidence that either of the most commonly studied topical antibiotics (mupirocin and fusidic acid) was more effective than the other (RR 1.03, 95% CI 0.95 to 1.11).

In 10 studies with 581 participants, topical mupirocin was shown to be slightly superior to oral erythromycin (pooled RR 1.07, 95% CI 1.01 to 1.13). There were no significant differences in cure rates from treatment with topical versus other oral antibiotics. There were, however, differences in the outcome from treatment with different oral antibiotics: penicillin was inferior to erythromycin, in 2 studies with 79 participants (pooled RR 1.29, 95% CI 1.07 to 1.56), and cloxacillin, in 2 studies with 166 participants (pooled RR 1.59, 95% CI 1.21 to 2.08).

There was a lack of evidence for the benefit of using disinfectant solutions. When 2 studies with 292 participants were pooled, topical antibiotics were significantly better than disinfecting treatments (RR 1.15, 95% CI 1.01 to 1.32).

The reported number of side-effects was low, and most of these were mild. Side-effects were more common for oral antibiotic treatment compared to topical treatment. Gastrointestinal effects accounted for most of the difference.

Worldwide, bacteria causing impetigo show growing resistance rates for commonly used antibiotics. For a newly developed topical treatment, retapamulin, no resistance has yet been reported.

Authors' conclusions

There is good evidence that topical mupirocin and topical fusidic acid are equally, or more, effective than oral treatment. Due to the lack of studies in people with extensive impetigo, it is unclear if oral antibiotics are superior to topical antibiotics in this group. Fusidic acid and mupirocin are of similar efficacy. Penicillin was not as effective as most other antibiotics. There is a lack of evidence to support disinfection measures to manage impetigo.

PLAIN LANGUAGE SUMMARY

Interventions for the skin infection impetigo

Impetigo causes blister-like sores. The sores can fill with pus and form scabs, and scratching can spread the infection. Impetigo is caused by bacteria. It is contagious and usually occurs in children. It is the most common bacterial skin infection presented by children to primary care physicians. Treatment options include topical antibiotics (antibiotic creams), oral antibiotics (antibiotics taken by mouth), and disinfectant solutions. There is no generally agreed standard treatment, and the evidence on what intervention works best is not clear.

We identified 68 randomised controlled trials comparing various treatments for impetigo. Altogether, these studies evaluated 26 oral treatments and 24 topical treatments, including placebo, and results were described for 5708 participants.

Overall, topical antibiotics showed better cure rates than topical placebo.

Two antibiotic creams, mupirocin and fusidic acid, are at least as effective as oral antibiotics where the disease is not extensive. There was no clear evidence that either of these most commonly studied topical antibiotics was more effective than the other.

Topical mupirocin was superior to the oral antibiotic, oral erythromycin.

We found that the oral antibiotic, oral penicillin, is not effective for impetigo, while other oral antibiotics (e.g. erythromycin and cloxacillin) can help.

It is unclear if oral antibiotics are superior to topical antibiotics for people with extensive impetigo.

There is a lack of evidence to suggest that using disinfectant solutions improves impetigo. When 2 studies with 292 participants were pooled, topical antibiotics were significantly better than disinfecting treatments.

Reported side-effects for topical treatments were mild and low in frequency; the treatments sometimes resulted in itching, burning, or staining. Oral antibiotics produced gastrointestinal complaints, such as nausea and diarrhoea, in 2% to 30% of participants, depending upon the specific antibiotic.

Worldwide, bacteria causing impetigo show growing resistance rates for commonly used antibiotics. For a newly developed topical treatment, retapamulin, no resistance has yet been reported.

BACKGROUND

Description of the condition

Biology and symptoms

Impetigo or impetigo contagiosa is a contagious superficial bacterial skin infection most frequently encountered in children. It is typically classified as either primary (e.g. direct bacterial invasion of previously normal skin), secondary, or common impetigo (where the infection is secondary to some other underlying skin disease that disrupts the skin barrier, such as scabies or eczema). Impetigo is also classified as bullous or non-bullous impetigo. Bullous impetigo simply means that the skin eruption is characterised by bullae (blisters). The term 'impetigo contagiosa' is sometimes used to mean non-bullous impetigo, and at other times it is used as a synonym for all impetigo.

Non-bullous impetigo is the most common form of impetigo. The initial lesion is a thin-walled vesicle on previously normal skin that rapidly ruptures. It then leaves superficial erosion covered with yellowish-brown or honey-coloured crusts. The crusts eventually dry, separate, and disappear, leaving a red mark that heals without scarring. The most frequently affected areas are the face and limbs. The lesions are sometimes painful. Usually, there are no systemic symptoms such as fever, malaise, or anorexia. Swelling of the lymph nodes draining the infected area of skin is common. It is believed that, in most cases, spontaneous resolution may be expected within two to three weeks without treatment but more prompt resolution occurs with adequate treatment. Diagnostic confusion can occur with a variety of skin disorders including shingles, cold sores, cutaneous fungal infections, and eczema (Hay 1998; Resnick 2000). Pyoderma is sometimes used as a synonym for impetigo in tropical countries. This is usually to denote streptococcal, as opposed to staphylococcal, impetigo.

Bullous impetigo is characterised by larger bullae or blisters that rupture less readily and can persist for several days. Usually there are fewer lesions and the trunk is affected more frequently than in non-bullous impetigo. Diagnostic confusion can occur with thermal burns, blistering disorders (e.g. bullous pemphigoid), and Stevens Johnson syndrome.

Causes

Staphylococcus aureus (S. aureus) is considered to be the main bacterium that causes non-bullous impetigo. However, *Streptococcus pyogenes (S. pyogenes),* or both *S. pyogenes* and *S. aureus,* are sometimes isolated from the skin. In moderate climates, staphylococcal impetigo is more common, whereas in warmer and more humid climates, the streptococcal form predominates. In moderate climates, the relative frequency of *S. aureus* infections has also changed with time (Dagan 1993). It was predominant in the 1940s and 1950s, after which Group A streptococci became more prevalent. In the past two decades, *S. aureus* has become more common again. Bullous impetigo is always caused by *S. aureus*.

Secondary impetigo may occur as a complication of many dermatological conditions (notably eczema). The eruption appears clinically similar to non-bullous impetigo. Usually *S. aureus* is involved. The underlying skin disease may improve with successful treatment of the impetigo, and the converse may also be true.

Complications of non-bullous impetigo are rare, but local and systemic spread of infection can occur that may result in cellulitis, lymphangitis, or septicaemia. Non-infectious complications of *S. pyogenes* infection include guttate psoriasis, scarlet fever, and glomerulonephritis (an inflammation of the kidney that can lead to kidney failure). It is thought that most cases of glomerulonephritis result from streptococcal impetigo rather than streptococcal throat infection, and this has always been an important rationale for antibiotic treatment. The incidence of acute glomerulonephritis has declined rapidly over the last few decades. Baltimore 1985 stated that the risk of developing glomerulonephritis is not altered by treatment of impetigo; however, certain subtypes of Group A streptococci are associated with a much greater risk (Dillon 1979b).

Epidemiology

In the Netherlands, most people with impetigo consult their general practitioner and only approximately 1% of the cases are referred to a dermatologist (Bruijnzeels 1993). Although the incidence of impetigo in general practice has been declining, recent data show an increase in consultations for impetigo (Koning 2006; Van den Bosch 2007). Impetigo is still a common disease particularly in young children. It is the third most common skin disorder in children after dermatitis/eczema and viral warts (Bruijnzeels 1993; Dagan 1993; Mohammedamin 2006). Impetigo is the most common skin infection that is presented in general practice by children aged one to four years of age (Mohammedamin 2006). In British general practice, 2.8% of children aged 0 to 4 and 1.6% aged 5 to 15 consult their GP about impetigo each year (McCormick 1995). In the Netherlands in the late 1980s, the consultation rate was 1.7% of all children under 18 years of age; this increased to 2.1% in 2001 (Koning 2006). Peak incidence occurs between the ages of one and eight years (Koning 2006). In some tropical or developing countries the incidence of impetigo seems to be higher than elsewhere (Canizares 1993; Kristensen 1991).

Description of the intervention

Management options for impetigo include the following:

1. no pharmacological treatment, waiting for natural resolution, hygiene measures;
2. topical disinfectants (such as saline, hexachlorophene, povidone iodine, and chlorhexidine);
3. topical antibiotics (such as neomycin, bacitracin, polymyxin B, gentamycin, fusidic acid, mupirocin, retapamulin, or topical steroid/antibiotic combination); and
4. systemic antibiotics (such as penicillin, (flu)cloxacillin, amoxicillin/clavulanic acid, erythromycin, and cephalexin).

The aim of treatment includes resolving the soreness caused by lesions and the disease's unsightly appearance (especially on the face), as well as preventing recurrence and spread to other people. An ideal treatment should be effective, cheap, easy to use, and accepted by people. It should be free from side-effects, and it should not contribute to bacterial resistance. For this reason, antibiotics should not have an unnecessarily broad spectrum (Espersen 1998; Smeenk 1999), and if a topical antibiotic is used, it should, preferably, not be one which may be needed for systemic use (Carruthers 1988; Smeenk 1999).

Waiting for natural resolution could be acceptable if the natural history were known and benign. Impetigo is considered to be self-

limiting by many authors (Hay 1998; Resnick 2000). However, there are no robust data on the natural history of impetigo. Reported cure rates of placebo creams vary from 8% to 42% at 7 to 10 days (Eells 1986; Ruby 1973). Topical cleansing used to be advised in the 1970s as an alternative for antibiotic treatment, but this was later said to be no more effective than placebo (Dagan 1992). Guidelines and treatment advice often do not mention topical cleansing as a treatment because the main concern is preventing the spread of the infection to other children.

A choice has to be made between topical and systemic antibiotic treatment, although in some situations clinicians prescribe both topical and systemic antibiotics. An advantage of the use of topical antibiotics is that the drug can be applied where it is needed, avoiding systemic side-effects such as gastrointestinal upset. Also, compliance may be better (Britton 1990).

The disadvantages of using topical antibiotics include the risks of developing bacterial resistance and sensitisation, e.g. developing an allergic contact dermatitis to one of the constituents of the topical preparation (Carruthers 1988; Smeenk 1999). This is especially common with the older antibiotics, such as gentamycin, bacitracin, and neomycin (Smeenk 1999). Some preparations (e.g. tetracycline) can cause staining of the skin and clothes.

Staphylococcal resistance against penicillin and erythromycin is common (Dagan 1992). Bacterial resistance against the newer topical antibiotics, such as mupirocin ointment and fusidic acid ointment, is increasing (Alsterholm 2010; de Neeling 1998). Another advantage of the newer topical antibiotics is that mupirocin is never, and fusidic acid not often, used systemically.

How the intervention might work

All treatment options listed above aim to either eradicate or prevent growth of the bacteria.

Why it is important to do this review

Guidelines concerning treatment vary widely - some recommend oral antibiotic treatment, others local antibiotic treatment or even just disinfection in mild cases (Hay 1998; Resnick 2000) - so clinicians have many treatment options. The evidence on what works best is not clear. There is potential conflict between what is in the best interest of the individual and what would best benefit the community in terms of cost and the increase in antibiotic resistance.

OBJECTIVES

To assess the effects of treatments for impetigo, including waiting for natural resolution.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials.

Types of participants

We included people who have impetigo or impetigo contagiosa diagnosed by a medically trained person (and preferably confirmed by bacterial culture). We recorded whether or not bacterial culture was performed. The diagnosis could be either non-bullous or bullous impetigo. Studies using a broader diagnostic category such as 'bacterial skin infections' or 'pyoderma' were eligible if a specific subgroup with impetigo could be identified, for which the results were separately described. Studies on secondary impetigo or impetiginised dermatoses were included.

Types of interventions

We included any program of topical or systemic (oral, intramuscular, or intravenous) treatment, including antibiotics, disinfectants, or any other intervention for impetigo, such as 'awaiting natural response'. We excluded studies that only compared different dosages of the same drug.

Types of outcome measures

Primary outcomes

1) Cure as defined by clearance of crusts, blisters, and redness as assessed by the investigator.

2) Relief of symptoms such as pain, itching, and soreness as assessed by participants.

Secondary outcomes

1) Recurrence rate.

2) Adverse effects such as pain, allergic sensitisation, and complications.

3) Development of bacterial resistance.

Search methods for identification of studies

We aimed to identify all relevant randomised controlled trials (RCTs) regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

We updated our searches of the following databases on 27 July 2010:

- the Cochrane Skin Group Specialised Register using the following search terms: (impetig* or pyoderma or ((staphylococc* or streptococc*) and skin and infection*)) and (therap* or treatment* or intervention*);
- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* using the search strategy in Appendix 1;
- MEDLINE (from 2005 to the present) using the search strategy in Appendix 2;
- EMBASE (from 2007 to the present) using the search strategy in Appendix 3; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982 to the present) using the search strategy in Appendix 4.

Please note: The UK and US Cochrane Centres have an ongoing project to systematically search MEDLINE and EMBASE for reports of trials which are then included in the CENTRAL database. Searching has currently been completed in MEDLINE, from inception to 2004 and in EMBASE, from inception to 2006. Further searches of these two databases to cover the years not searched by

the UK and US Cochrane Centres for CENTRAL were undertaken for this review as described above.

A final prepublication search for this review was undertaken on 16 August 2011. Although it has not been possible to incorporate RCTs identified through this search within this review, relevant references are listed under Studies awaiting classification. They will be incorporated into the next update of the review.

Ongoing Trials

We updated our searches of the following ongoing trials databases on 3 August 2010, using the terms 'impetigo' and 'pyoderma':

- The metaRegister of Controlled Trials (www.controlled-trials.com).
- The US National Institutes of Health Ongoing TrialsRegister (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- The Ongoing Skin Trials Register (www.nottingham.ac.uk/ongoingskintrials).

Searching other resources

Handsearching

We handsearched the Yearbook of Dermatology (1938 to 1966) and the Yearbook of Drug Therapy (1949 to 1966) for the pre-PubMed era.

References from published studies

We checked references from published studies, including secondary review articles, for further studies.

Unpublished literature

We corresponded with authors and pharmaceutical companies to search for unpublished studies and grey literature.

Language

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two authors (JCvdW and SK or RvdS) independently read all abstracts or citations of trials. If one of the authors thought the article might be relevant, a full copy of the article was acquired for further data collection. The reasons for exclusion were recorded for every excluded abstract or citation. Only full reports were included. Two authors independently screened all full-copy articles (LvSS, SK, RvdS, JCvdW). The articles were selected according to the inclusion criteria. Reasons for exclusion were recorded on a specially-designed registration form (see the 'Characteristics of excluded studies' table). In the case of doubt, the opinion of a third author was obtained. Many trials studied a range of (skin) infections including impetigo. Frequently, the results of the subgroup of impetigo participants were not reported separately. In these studies, provided they were published in the last 10 years, we contacted trial authors and asked them to provide the results of the subgroup of impetigo participants. We obtained data in this way in only two instances (Blaszcyk 1998; Claudy 2001).

Data extraction and management

Two authors (ADM and CCB), using a pre-piloted data abstraction form, carried out the full data extraction. The form contained key elements such as time and setting of the study, participant characteristics, bacterial characteristics, type of interventions, outcomes, and side-effects. We resolved disagreements with the help of a third author (SK).

For this update, RvdS and JCvdW carried out data extraction from newly included papers. When studies assessed outcome measures more than once, we included the assessment that was nearest to one week after the start of therapy. When studies had more than two arms and two of these arms were different dosages of the same drug, we combined these arms.

Assessment of risk of bias in included studies

Assessment of methodological quality

Two independent authors (JCvdW, RvdS and/or AV) assessed the methodological quality of all trials according to the updated guidelines (Higgins 2008). Because we could not read the Japanese study by Ishii 1977, this 'Risk of bias' table was completed by Tetsuri Matsumura. The two studies on which authors of this review were co-authors (Koning 2003; Koning 2008) were assessed by other authors. The items that were addressed are shown in the 'Risk of bias' table. For feasibility reasons, the methodological quality assessment was not performed under masked conditions. There is no consensus over whether assessment should be done blinded for authors, institutions, journal, or publication year (Jadad 1998).

Unit of analysis issues

In the case of studies with more than two treatment arms, we deemed that pooling these studies under separate comparisons, without adjustment, would result in unit-of-analysis errors (overcounting). Should this have occurred, the problem was to be solved by dividing the group size by the number of comparisons.

Assessment of heterogeneity

We used the I^2 statistic to assess statistical heterogeneity, with I^2 statistic > 50% regarded as substantial heterogeneity.

Data synthesis

Where there was no statistical evidence of heterogeneity we used the fixed-effect model to estimate effects. Otherwise, we used the random-effects model. For dichotomous outcomes we reported risk ratios with 95% confidence intervals.

Sensitivity analysis

We prespecified the following factors for sensitivity analyses:

1. the quality of the studies;
2. whether there was observer blinding;
3. whether there was just a clinical diagnosis or bacterial swab confirmation;
4. primary versus secondary impetigo;
5. bullous versus non-bullous; and
6. staphylococcal or streptococcal predominance.

During the update, we decided that an overall quality score per study was not useful. Furthermore, most trials were observer-blind, took bacterial swabs, studied primary impetigo, and had staphylococcal predominance. Sensitivity analyses for these items were, therefore, not possible.

When we analysed the data we decided to consider the results for bullous and non-bullous impetigo separately.

RESULTS

Description of studies

Results of the search

Our initial search identified approximately 700 papers, 221 of which were selected for full copy reading. For this update, we identified more than 1000 additional papers. Two reviewers screened titles and abstracts, after which, approximately, 60 papers were studied in full copy.

Included studies

For the first version of the review we included 56 papers describing 57 trials. This update identified 12 additional studies, of which 2 were published before 2000 (Farah 1967; Ishii 1977). One study, which was previously included, was excluded because it turned out not to be a randomised trial (Park 1993), bringing the total number of included studies to 68. The lists of ongoing studies (Ongoing studies) and studies awaiting assessment (Studies awaiting classification) show studies that might be eligible for a future update of this review. Regarding the excluded studies, we only report on the most relevant ones (Excluded studies; Characteristics of excluded studies).

Most trials were reported in the English language. Four included studies were reported in Japanese, and one paper each was reported in Thai, Portuguese, Spanish, French, and Danish (some of these had abstracts and tables in English). Trials in Russian, Chinese, German, and French were among those that were excluded (not for language reasons). In instances where none of the authors were competent in the language of the paper, translators provided assistance.

We found an appreciable number of studies from the early 1940s (e.g. MacKenna 1945). These studies were often carried out in military populations, in which impetigo was a frequent disease at the time. These study reports did not meet the inclusion criteria of our review because of inadequate randomisation. The distribution of the included studies by decade is as follows: 1960s - 1 study, 1970s - 5 studies (7%), 1980s - 31 studies (46%), 1990s - 20 studies (29%), and 2000 to 2008 - 11 studies (16%). Five included studies evaluating mupirocin were presented at an international symposium in 1984; we found no publication other than the conference proceedings for three of these (Kennedy 1985; Rojas 1985; Wainscott 1985). Two were published elsewhere as well (Eells 1986; Gould 1984).

Design

All studies were parallel group trials, but there were important design differences between the studies. As mentioned before, many trials included participants with infections other than impetigo, while some trials studied only impetigo. Ages of included participants differed widely, as some studies were carried out exclusively in either adults or children. The average age of study participants in trials that studied a range of skin infections was usually higher than in studies focusing on impetigo alone. With the exception of four studies (Faye 2007; Ishii 1977; Rice 1992; Vainer 1986), all studies performed bacteriological investigations. Although a number of studies explicitly stated that participants with a negative culture were excluded, other studies may also have excluded culture negative participants without reporting those exclusions. No study reported a predominantly streptococcal impetigo. The only studies not to report a preponderance of staphylococcal impetigo were Mertz 1989 and Ruby 1973 (carried out in Puerto Rico and Texas respectively).

Sample sizes

The 68 studies had a total of 5578 evaluable participants; this is an average of 82 participants and a median of 60.5 participants per study (see the 'Characteristics of included studies' tables). In 23 studies the number of participants with impetigo was less than 50; in 10 studies it was less than 20.

Setting

Twenty-nine of the studies were carried out in North America (in 13 Canadian/Northern states, in 8 Southern states, in 8 multicentres), 15 in Europe, 9 in Central/South America, 10 in Asia, 1 in Africa, and 4 were worldwide multicentre trials. Most studies were carried out in hospital out-patient clinics (paediatrics or dermatology, 60 studies), but some were carried out in general practice.

Participants

Only three studies exclusively addressed participants with bullous impetigo (Dillon 1983; Ishii 1977; Moraes Barbosa 1986). Seven trials included both bullous and non-bullous impetigo participants (Barton 1989; Ciftci 2002; Dagan 1992; Koning 2008; Kuniyuki 2005; Oranje 2007; Pruksachat 1993). Three studies on secondary impetigo were included (Fujita 1984; Rist 2002; Wachs 1992). Three other trials included both primary and secondary impetigo participants (Faye 2007; Gonzalez 1989; Tamayo 1991). Thirty-nine trials studied impetigo alone whereas 29 trials studied participants with a range of (usually skin) infections, impetigo being 1 of them. This was the typical study design when a new antibiotic was studied. This type of study design imposed problems in retrieving outcome data as the outcomes were often presented for all the participants together. We included these studies only if the main outcome measure was presented separately for the subgroup of impetigo participants.

Interventions

The 68 trials evaluated 50 different treatments (26 oral treatments and 24 topical treatments - both including placebo). The systemic treatments that were studied were all administered orally (tablets). A total of 74 different comparisons were made. Some comparisons were made in several studies; some studies made more than one comparison. Sixty-eight comparisons were made only once. Six different comparisons were made in more than 1 trial, especially when topical mupirocin was studied (topical mupirocin versus oral erythromycin was considered in 10 studies, mupirocin versus fusidic acid was considered in 4 studies, mupirocin versus placebo was considered in 3 studies). For each of these comparisons we pooled the outcomes of the different studies (see Data and analyses).

The most common type of comparison was between 2 different oral antibiotic treatments (29 studies including duplicates). Cephalosporins (15 studies) and macrolide antibiotics, especially erythromycin and azithromycin (9 studies), were most often involved. A topical antibiotic treatment was compared with an oral antibiotic treatment in 22 studies. Nineteen of these comparisons contained erythromycin, mupirocin, or both.

Only two trials studied antiseptic or disinfecting treatments (Christensen 1994; Ruby 1973).

Only seven placebo controlled trials were found (Eells 1986; Gould 1984; Ishii 1977; Koning 2003; Koning 2008; Rojas 1985; Ruby 1973). The latter is the only trial that compared an oral treatment with placebo.

Three studies had three arms but the treatment in two of these were different dosages of the same drug (Blaszcyk 1998; Bucko 2002a; Bucko 2002b). We combined these arms. Nine other studies had more than two arms but with different treatments: three arms (Bass 1997; Demidovich 1990; Dux 1986; Rodriguez-Solares 1993; Vainer 1986; Wachs 1976), four arms (Kuniyuki 2005; Moraes Barbosa 1986), and five arms (Ruby 1973). Only two of the comparisons in these multiple-arm studies could be pooled with other studies: erythromycin versus penicillin V from Demidovich 1990, and mupirocin versus erythromycin from Dux 1986. For this reason we refrained from adjusting for multiple treatment comparisons.

Outcomes

Cure as assessed by investigator was our main outcome measure. This was often not defined. Researchers sometimes combined the categories 'cured' and 'improved' and presented those participants as one group. The length of follow-up varied widely, and it was sometimes not even specified; however, we tried to retrieve the data for follow up as close as possible to seven days after the start of treatment. The development of bacterial resistance to the study drug was reported in only 10 studies.

Excluded studies

One hundred and sixty-five of the studies did not meet the inclusion criteria for the first version of the review, and 33 more were excluded when updating the review (see the 'Characteristics of excluded studies' tables). The most common reasons included the following: the study was not about impetigo, the outcomes of impetigo participants were not reported separately, or studies were not randomised.

Studies awaiting classification

In the previous version of this review, four studies were awaiting classification. For this update two of these studies were included (Ciftci 2002; Claudy 2001) and two were excluded (Liu 1986; Parish 2000).

Ten studies that were found during the update process are listed in the 'Characteristics of studies awaiting classification' tables, as are a further 6 studies that were identified at the prepublication search. We are currently unable to include or exclude these due to insufficient information about them. We hope to fully incorporate them into future updates of this review.

Ongoing studies

Seven studies that were found during the update process are listed in the 'Characteristics of ongoing studies' tables. These will be fully incorporated into future updates of this review when they are completed.

Risk of bias in included studies

For many of the items that were assessed, the studies did not provide enough information (Figure 1; Figure 2).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

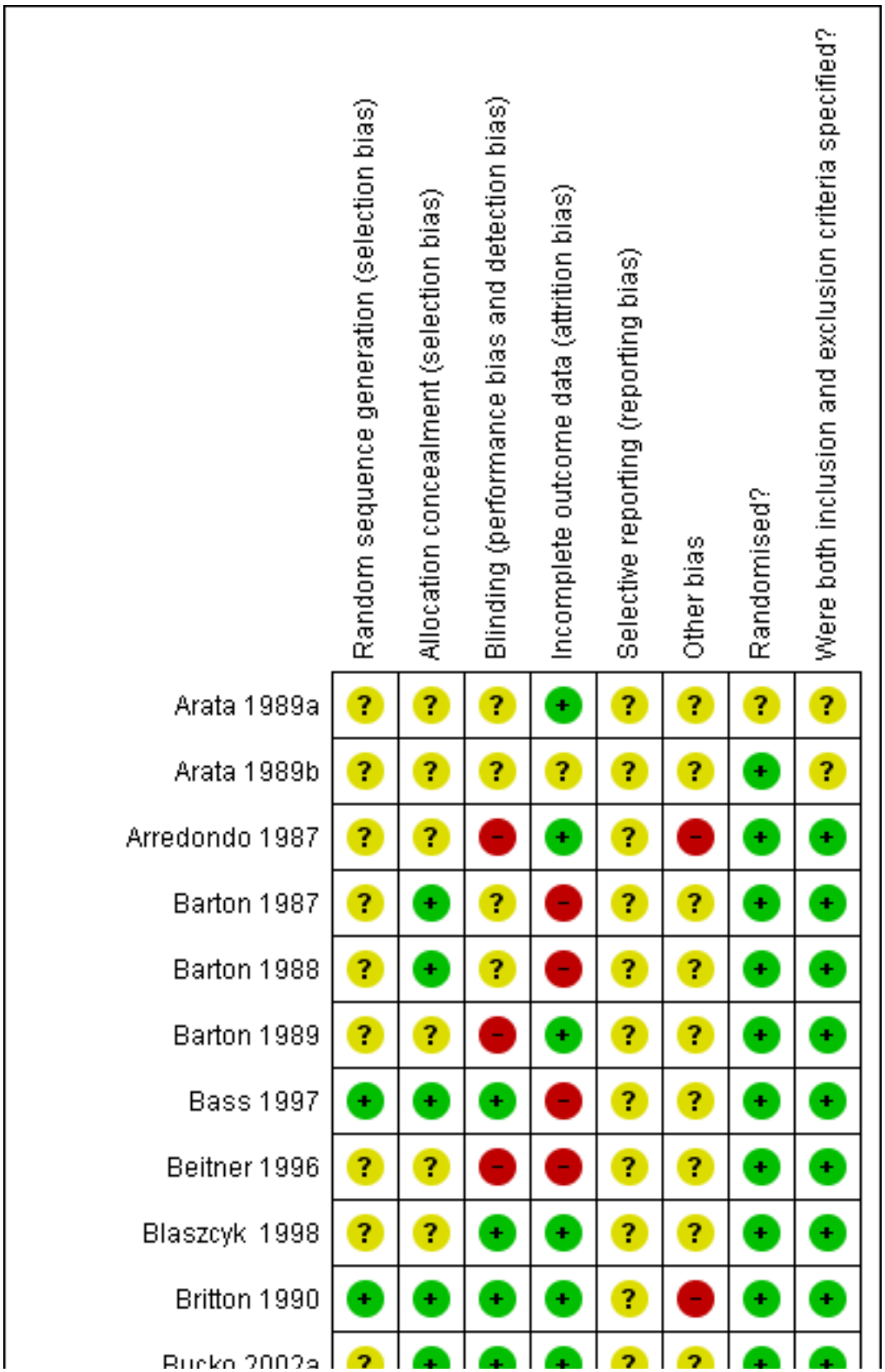


Figure 1. (Continued)

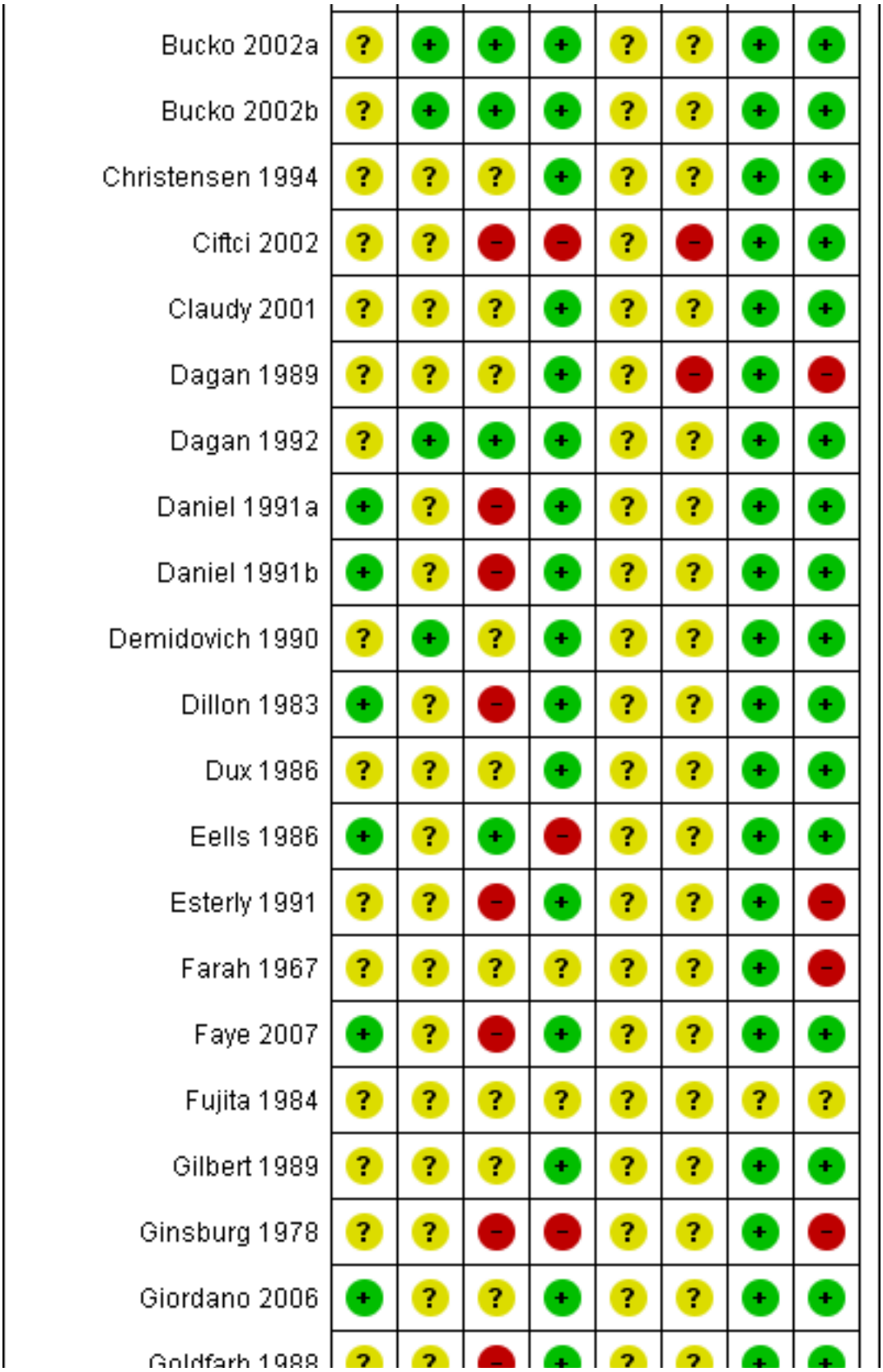


Figure 1. (Continued)

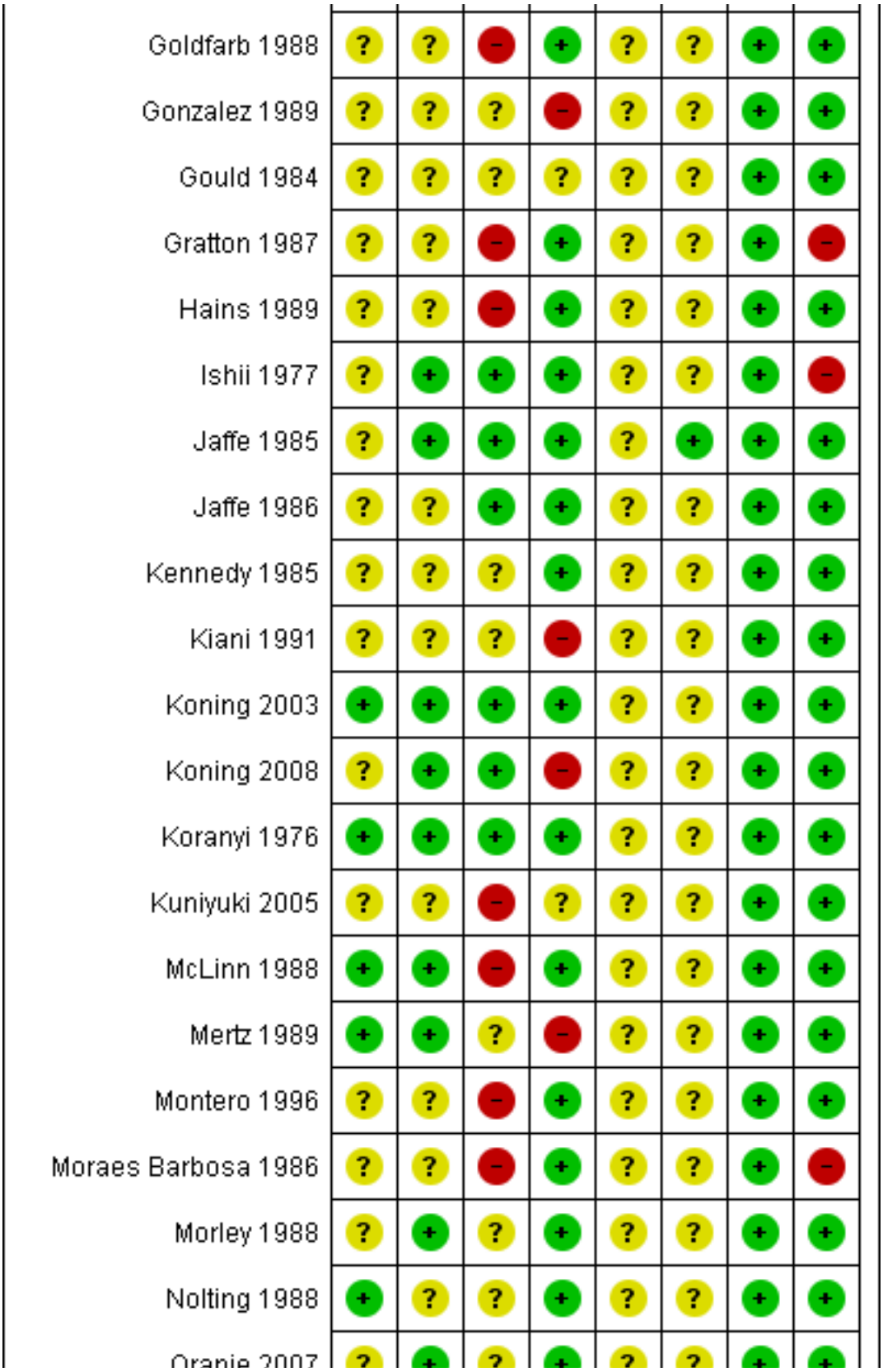


Figure 1. (Continued)

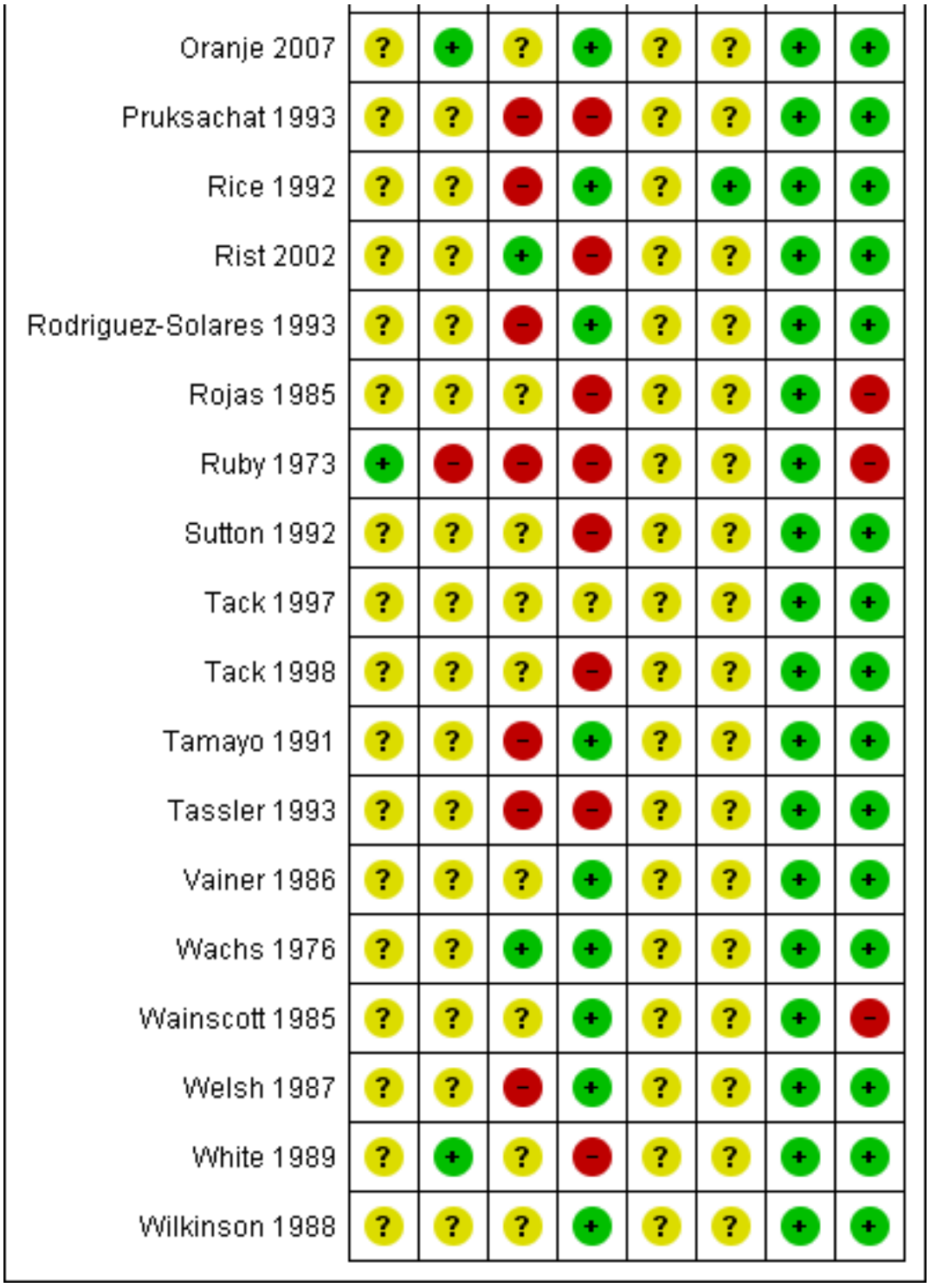
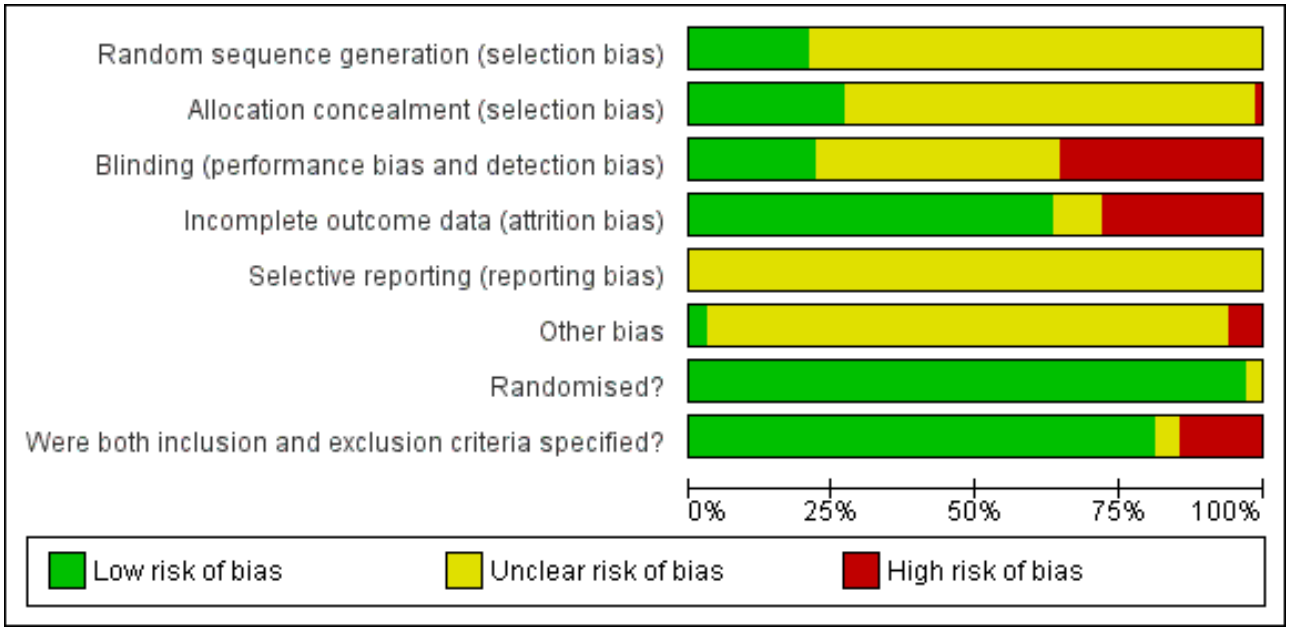


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Sequence generation

Fourteen of the studies reported an adequate generation of the randomisation scheme. All other papers did not report on this item.

Allocation

All but two of the included studies were described as randomised as this was a selection criterion. For two papers in Japanese, this was unclear, and these papers were given the benefit of the doubt (see Figure 1). Most papers did not describe the method of randomisation in detail, so the method could not be judged as appropriate. Only 19 of the 68 studies provided information on allocation concealment. In most cases (18 of 19), treatment allocation was considered to be concealed.

Blinding

In many cases it was not clear whether the participant, the caregiver, or the outcome assessor were blinded. A total of 15 studies were considered to be adequately blinded (see Figure 1). In 24 studies, at least 1 party was considered not to be blinded. In 29 papers, the information was insufficient to judge blinding.

Inclusion and exclusion criteria of the trials

In 10 of our included studies, the inclusion and exclusion criteria of the trial were not specified in more detail than saying 'patients with impetigo' (see Figure 1).

Incomplete outcome data

In some studies, high numbers lost to follow up were recorded. Thirty-four studies either included an intention-to-treat analysis or had fewer than 10% dropouts balanced between groups. For some other studies, an intention-to-treat analysis could be calculated from the data presented in the study.

Effects of interventions

Primary outcomes: 1) clinical cure

The first primary outcome was *clinical cure (or improvement)* as assessed by the investigator. When this was assessed more than once, we only included the assessment that was nearest one week from commencement of treatment.

Under the following two main headings ('non-bullous impetigo' and 'bullous impetigo') we have grouped all studies that either included only primary impetigo, combined primary and secondary impetigo, or did not specify whether participants had primary or secondary impetigo. The third heading 'secondary impetigo' addresses all studies that focused exclusively on secondary impetigo (see Background for an explanation).

(a) Non-bullous impetigo

(i) Topical antibiotics

Topical antibiotics versus placebo (six studies, four comparisons)

Overall topical antibiotics showed better cure rates or more improvement than placebo (pooled risk ratio (RR) 2.24, 95% CI 1.16 to 3.13 using a random-effects model, I^2 = 53%) (see Analysis 1.1). This result was consistent for mupirocin (RR 2.21, 95% CI 1.59 to 3.05; 3 studies - Eells 1986; Gould 1984; Rojas 1985) (see Analysis 1.1), fusidic acid (RR 4.42, 95% CI 2.39 to 8.17; 1 study - Koning 2003) (see Analysis 1.1), and retapamulin (RR 1.64, 95% CI 1.30 to 2.07; 1 study - Koning 2008) (see Analysis 1.1). In one small study (Ruby 1973), bacitracin did not show a significant difference in cure rate compared with placebo (RR 3.71, 95% CI 0.16 to 85.29) (see Analysis 1.1).

Topical antibiotic versus another topical antibiotic (14 studies, 15 comparisons)

Only one topical antibiotic showed superiority over another topical antibiotic - in a single study: gentamycin over neomycin (RR 1.43,

95% CI 1.03 to 1.98; Farah 1967) (see Analysis 2.1). Also from a single study, the difference between retapamulin over fusidic acid was not statistically significant (RR 1.05, 95% CI 1.00 to 1.11; Oranje 2007) (see Analysis 2.1). There were 12 different comparisons: 4 studies (Gilbert 1989; Morley 1988; Sutton 1992; White 1989) compared mupirocin with fusidic acid (RR 1.03, 95% CI 0.95 to 1.11) (see Analysis 2.1), and the remaining 11 were all only represented by a single study.

Topical antibiotics versus oral (systemic) antibiotics (16 studies, 17 comparisons)

Pooling 10 studies which compared mupirocin with oral erythromycin showed significantly better cure rates, or more improvement, with mupirocin (RR 1.07, 95% CI 1.01 to 1.13) (see Analysis 3.1). However, no significant differences were seen between mupirocin and dicloxacillin (Arredondo 1987), cephalexin (Bass 1997), or ampicillin (Welsh 1987). Bacitracin was significantly worse than oral cephalexin in one small study (Bass 1997), but no difference was seen between bacitracin and erythromycin (Koranyi 1976), or penicillin (Ruby 1973).

A sensitivity analysis on the influence of blinding the outcome assessor on the comparison of mupirocin versus erythromycin (10 studies) revealed that there was no clear relationship between blinding of the outcome assessor and the outcome.

Pooling the 2 studies with observer blinding (Britton 1990; Dagan 1992) showed high heterogeneity (I^2 statistic = 79%) and resulted in a non-significant difference between the 2 drugs (random-effects model, RR 1.12, 95% CI 0.86 to 1.46) (see Analysis 3.2).

Topical antibiotics versus disinfecting treatment (two studies)

In one study (Ruby 1973), no statistically significant difference in cure/improvement was seen when bacitracin was compared to hexachlorophene (RR 3.71, 95% CI 0.16 to 85.29) (see Analysis 4.1). In another study (Christensen 1994), there was a tendency for fusidic acid cream to be more effective than hydrogen peroxide, but this just failed to reach statistical significance (RR 1.14, 95% CI 1.00 to 1.31) (see Analysis 4.1). When the 2 studies were pooled, topical antibiotics were significantly better than disinfecting treatments (fixed-effect model, RR 1.15, 95% 1.01 to 1.32, I^2 statistic 0%) (see Analysis 4.1).

Topical antibiotic versus antifungal (one study)

Only one study compared a topical antibiotic to an antifungal, comparing topical mupirocin to topical terbinafine (Ciftci 2002). No statistical difference was seen (RR 1.39, 95% CI 0.98 to 1.96) (see Analysis 5.1).

Topical antibiotic + oral antibiotic vs topical antibiotic + oral antibiotic (one study, three comparisons)

In a four-armed study, three arms addressed the following combinations of a topical antibiotic and an oral antibiotic: topical tetracycline combined with oral cefdinir compared to topical tetracycline combined with oral minomycin, topical tetracycline combined with oral cefdinir compared to topical tetracycline combined with oral fosfomycin, and topical tetracycline combined with oral minomycin compared to topical tetracycline combined with oral fosfomycin (Kuniyuki 2005). None of the three comparisons showed a statistically significant difference (see Analysis 6.1).

Topical antibiotic versus topical antibiotic + oral antibiotic (one study, three comparisons)

The fourth arm of the study described under the previous heading (Kuniyuki 2005) was tetracycline. None of the comparisons with the other three treatments (see above) showed a statistically significant difference (see Analysis 7.1).

(ii) Oral antibiotics

Oral antibiotics versus placebo (one study)

A single study (Ruby 1973) found no significant difference between oral penicillin and placebo (RR 7.74, 95% CI 0.43 to 140.26) (see Analysis 8.1).

Oral antibiotic versus another oral antibiotic: cephalosporin versus another antibiotic (six studies)

All comparisons consisted of single studies (or arms of a single study); only one comparison - cephalexin versus penicillin - showed a significant difference (Demidovich 1990) (see Analysis 9.1).

Oral antibiotic versus another oral antibiotic: one cephalosporin versus another cephalosporin (seven studies)

No significant differences were seen between cephalexin and cefadroxil (Hains 1989), cefdinir (Giordano 2006; Tack 1997; Tack 1998); cefaclor and cefdinir (Arata 1989a), or cefditoren and cefadroxil (Bucko 2002b). Cefditoren turned out to be less effective than cefuroxime (Bucko 2002a) (see Analysis 10.1).

Oral antibiotic versus another oral antibiotic: macrolides (erythromycin, azithromycin, clindamycin) versus penicillins (penicillin V, dicloxacillin, amoxacillin, cloxacillin, flucloxacillin) (seven studies)

In two studies (Barton 1987; Demidovich 1990), erythromycin showed a better cure rate or more improvement than penicillin (pooled fixed-effect model, RR 1.29, 95% CI 1.07 to 1.56, I^2 statistic 0%) (see Analysis 11.1). The other five comparisons consisted of single studies, and they did not show significant differences between macrolides and penicillins.

Oral antibiotic versus another oral antibiotic: macrolide versus another macrolide (one study)

In a single study (Daniel 1991a), no difference in cure rate or improvement was seen between azithromycin and erythromycin (RR 1.18, 95% CI 0.88 to 1.58) (see Analysis 12.1).

Oral antibiotic versus another oral antibiotic: penicillin versus other oral antibiotics (including other penicillins) (four studies)

In 1 study (Dagan 1989), amoxicillin plus clavulanic acid showed a better cure rate than amoxicillin alone (RR 1.40, 95% CI 1.04 to 1.89) (see Analysis 13.1), but when amoxicillin plus clavulanic acid was compared with fleroxacin in another study (Tassler 1993), no significant difference was seen (RR 1.14, 95% CI 0.80 to 1.62) (see Analysis 13.1). Cloxacillin was significantly superior to penicillin in 2 studies (Gonzalez 1989; Pruksachat 1993) although these studies were statistically heterogeneous (I^2 statistic 57%) (pooled RR 1.59, 95% CI 1.21 to 2.08) (see Analysis 13.1).

Other comparisons of oral antibiotics (two studies)

In two studies (Arata 1989b; Claudy 2001), no difference in cure rates/improvement could be detected between lomefloxacin and

norfloxacin nor between (oral) fusidic acid and pristinamycin (see Analysis 14.1).

Oral antibiotics versus disinfecting treatments (one study)

In a single small study (Ruby 1973), no difference in cure rates/improvement could be detected between penicillin and hexachlorophene (RR 7.74, 95% CI 0.43 to 140.26) (see Analysis 15.1).

(iii) Disinfecting treatments

Disinfecting treatments versus placebo (one study)

In a single small study (Ruby 1973), no participants in either the hexachlorophene (n = 11) or placebo group (n = 13) showed cure or improvement. Comparisons of disinfecting treatments with antibiotics are given above.

(b) Bullous impetigo

(i) Topical antibiotics

Topical antimicrobial versus placebo (one study)

In one study (Ishii 1977), topical Eksalbe simplex (a drug containing killed *Eschelichia, Staphylococcus, Streptococcus, and Pseudomonas*) was compared to placebo. The active drug turned out to be superior (cure/improvement RR 2.30, 95% CI 1.10 to 4.79) (see Analysis 16.1).

Topical antibiotics versus other topical antibiotics (one study, three comparisons)

In a small study (Moraes Barbosa 1986), fusidic acid was significantly more effective than both neomycin/bacitracin (RR 10.00, 95% CI 1.51 to 66.43) (see Analysis 17.1) and chloramphenicol (RR 5.00, 95% CI 1.38 to 18.17) (see Analysis 17.1). In the same study, no difference was detected between chloramphenicol and neomycin/bacitracin (RR 2.00, 95% CI 0.21 to 19.23) (see Analysis 17.1).

Topical antibiotics versus oral antibiotics (one study, three comparisons)

The same study (Moraes Barbosa 1986) showed that neomycin/bacitracin was significantly less effective than oral erythromycin (RR 0.14 95% CI 0.02 to 0.99) (see Analysis 18.1). There was no significant difference between either erythromycin and fusidic acid (RR 1.43, 95% CI 0.83 to 2.45) (see Analysis 18.1) or chloramphenicol (RR 0.29, 95% CI 0.07 to 1.10) (see Analysis 18.1).

(ii) Oral antibiotics

Oral antibiotic versus another oral antibiotic (one study)

No significant difference was seen between cephalexin and dicloxacillin (Dillon 1983; RR 1.17, 95% CI 0.95 to 1.45) (see Analysis 19.1).

(c) Secondary impetigo

(i) Topical antibiotics

Topical antibiotic versus oral antibiotic (one study)

No significant difference was seen between mupirocin and cephalexin (Rist 2002) (see Analysis 20.1).

Antibiotic versus steroid versus antibiotic plus steroid (one study)

In a three-armed study (Wachs 1976), the comparisons of betamethasone with gentamycin alone or with betamethasone plus gentamycin did not show significant differences (see Analysis 21.1 and Analysis 22.1). The combination of betamethasone and gentamycin cream was significantly more effective than gentamycin alone (RR 2.43, 95% CI 1.29 to 4.57) (see Analysis 23.1).

(ii) Oral antibiotics

In a very small study, no significant difference was detected between cephalexin and enoxacin (Fujita 1984) (see Analysis 24.1).

Primary outcomes: 2) relief of symptoms

The second primary outcome was relief of symptoms, such as pain, itching, and soreness, as assessed by study participants. Although some studies asked about overall satisfaction, acceptability, or treatment preference (McLinn 1988; Rice 1992; Rist 2002; Sutton 1992; White 1989), only one study asked participants to rate their symptoms at follow-up (Giordano 2006). However, this was a study addressing not only impetigo but other skin infections as well, and results for this outcome were not reported for impetigo separately.

Secondary outcomes: 1) recurrence rate

No relevant data were provided by any study for this outcome.

Secondary outcomes: 2) adverse effects

(i) Topical antibiotics

The trials included in this review usually reported few, if any, side-effects from topical antibiotics (see Table 1). The studies comparing mupirocin, bacitracin, and placebo reported none (Eells 1986; Ruby 1973). The study that compared fusidic acid to placebo recorded more side-effects in the placebo group (Koning 2003). Three of 4 studies comparing mupirocin with fusidic acid recorded side-effects: minor skin side-effects were reported for mupirocin by 10 out of 368 participants (3%) and for fusidic acid by 4 out of 242 participants (2%). The study that compared retapamulin to placebo found more itching in the group treated with retapamulin (7% vs 1%; P = 0.17) (Koning 2008). In the other study of retapamulin, this side-effect was reported in less than 1% of cases (Oranje 2007). Most other trials comparing topical antibiotics reported no side-effects or reported minor skin side-effects in low numbers (less than 5% of participants).

Topical versus oral treatments

Of the 10 trials comparing erythromycin with mupirocin, 9 reported side-effects. All trials recorded more side-effects from erythromycin, with the exception of two trials (Britton 1990 - equally divided minor gastrointestinal side-effects - and Rice 1992 - nil reported). Gastrointestinal side-effects (nausea, stomach ache, vomiting, diarrhoea) were recorded in 80 out of 297 participants (27%) in the erythromycin groups, versus 17 out of 323 participants (5%) in the mupirocin groups. Skin side-effects (itching, burning) were recorded in 5 out of 297 participants (2%) in the erythromycin groups versus 23 out of 323 participants (7%) in the mupirocin groups. Most other trials comparing topical and oral antibiotics did not record data on side-effects (see Table 1).

(ii) Oral antibiotics

Eleven of the 31 trials comparing oral antibiotics did not report on side-effects (see Table 1). Three of the 6 trials that studied erythromycin recorded side-effects; the highest frequency was reported by Faye 2007: 11/65 participants reported gastrointestinal side-effects (mainly diarrhoea). The other trials, usually making unique comparisons, mainly reported gastrointestinal side-effects in small percentages. In five trials, a considerable difference in side-effects was reported. Gastrointestinal complaints were recorded in 1 out of 113 participants (10%) in the enoxacin group compared to 4 out of 110 participants (4%) in the cefalexin group (Fujita 1984). Fourteen out of 327 (4%) of the cefadroxil-treated participants versus 2 out of 234 (1%) flucloxacillin-treated participants had 'severe' side-effects, such as stomach ache, rash, fever, and vomiting (Beitner 1996). Cefaclor caused more diarrhoea than amoxicillin plus clavulanic acid (5 out of 16 participants (31%) vs 2 out of 18 participants (11%)) (Jaffe 1985). Pristinamycin caused more upper and lower gastrointestinal side-effects than oral fusidic acid (12% vs 7% and 17% vs 2%, respectively) (Claudy 2001). Finally, the clindamycin group of participants reported more side-effects (any side-effect) than the dicloxacillin-treated group (Blaszcyk 1998).

(iii) Disinfecting treatments

Eleven per cent of the participants using hydrogen peroxide cream reported mild side-effects (not specified) versus seven per cent in the fusidic acid group (Christensen 1994). No participant was withdrawn from the study because of side-effects. No adverse effects of scrubbing with hexachlorophene were recorded (Ruby 1973) (see Table 1).

Secondary outcomes: 3) Development of bacterial resistance

Most studies either did not report on susceptibility of isolated pathogens to the study drugs or presented only baseline data. Ten studies provided information on the development of resistance to the study drug during the study period (Barton 1988; Bucko 2002a; Bucko 2002b; Dagan 1992; Giordano 2006; Goldfarb 1988; Gould 1984; Tack 1998; Tassler 1993; White 1989). In most of these studies, none or only a few of the participants' pathogens had developed resistance. The only exception was Dagan 1992, where 14/18 (78%) of positive cultures after 3 days of follow-up showed resistance to erythromycin, compared to 27/91 (28%) at baseline. The other study that included erythromycin (Goldfarb 1988) showed only 3% (1/32) resistance at follow-up.

DISCUSSION

Summary of main results

Overall, topical antibiotics showed better cure rates than topical placebo. No differences were found between the two most studied topical antibiotics: mupirocin and fusidic acid. Topical mupirocin was superior to oral erythromycin. In most other comparisons, topical and oral antibiotics did not show significantly different cure rates, nor did most trials comparing oral antibiotics. Penicillin V was inferior to erythromycin and cloxacillin, and there is a lack of evidence to suggest that using disinfectant solutions improves impetigo.

The reported number of side-effects was low. Oral antibiotic treatment caused more side-effects, especially gastrointestinal ones, than topical treatment. A striking finding is that the trials comparing erythromycin with mupirocin recorded more (gastrointestinal) side-effects in the erythromycin group than the trials that compared erythromycin with other oral antibiotics.

Overall completeness and applicability of evidence

The large number of treatments evaluated (50) supports the view that there is no widely accepted standard therapy for impetigo. Most studies did not contribute clear answers about the vast choice of treatment options. Many of the studies were underpowered; this is partly due to the fact that many trials included several skin infections, impetigo being only one of them (these studies are directed at the drug rather than at the disease). In many cases, significant differences became insignificant when impetigo participants were considered after excluding participants with other sorts of infection. Another drawback of this type of study is that the age of participants is much higher than the typical age at which people contract impetigo (e.g. Blaszcyk 1998; Bucko 2002a; Bucko 2002b; Kiani 1991). The dosage of studied antibiotics may differ between studies, complicating the comparability of studies; however, the same doses were usually used (e.g. erythromycin 40 mg/kg/day). Cure rates of specific treatments can be different between studies, e.g. of fusidic acid and mupirocin (Sutton 1992; White 1989). This may be explained by the fact that investigations were done in different regions and times, and inclusion criteria differed.

Little is known about the 'natural history' of impetigo. Therefore, the paucity of placebo-controlled trials is striking, given that impetigo can be considered a minor disease. Only seven placebo-controlled studies have been conducted (Eells 1986; Gould 1984; Ishii 1977; Koning 2003; Koning 2008; Rojas 1985; Ruby 1973). The 7-day cure rates of placebo groups in these studies varied but can be considerable (0% to 42%).

The disinfectant agents, such as povidone iodine and chlorhexidine, recommended in some guidelines (Hay 1998; Resnick 2000), usually as supplementary treatment, have been inadequately studied and not compared to placebo treatment. Hydrogen peroxide cream was not significantly less effective than fusidic acid (cure rate 72% versus 82%) in a relatively large trial (Christensen 1994). We judged that blinding in this trial was inadequate.

There is a commonly accepted idea that more serious forms of impetigo (e.g. participants with extensive lesions, general illness, fever) need oral rather than topical antibiotic treatment. This principle cannot be evaluated using the data included in our review as trials that study local treatments usually exclude participants with more serious forms of impetigo.

One of our primary outcomes was relief of symptoms, such as pain, itching, and soreness, as assessed by participants (or parents). Surprisingly, only one of the studies addressed this outcome (Giordano 2006).

Resistance patterns of staphylococci - which causes impetigo - change over time. Outcomes of studies dating back more than 10 years, which form the majority of trials in this review, may not be applicable to the current prevalence of infecting agents. Also, resistance between regions and countries may vary considerably. Thus, up-to-date, local characteristics and resistance patterns

of the causative bacteria should always be taken into account when choosing antibiotic treatment. In addition, health authorities and other relevant bodies may advise against prescribing certain antibiotics for impetigo, in order to restrict the development of bacterial resistance and reserve these drugs for more serious infections.

Quality of the evidence

Although the total number of randomised trials we identified was considerable, the average number of participants per study was small. In this update, the newly added studies made this average increase from 62 to 84 per study. This was partly due to studies that assessed a range of infections and randomised a large number of participants, but in which those with impetigo were only a minority. Through the years, we found an increase in the quality of the studies; the average number of items scored positively increased from less than three in the 1970s to almost five for studies published in the new millennium. This is a problem shared with many other reviews. Details of the design of the studies were often lacking in the published reports, leading to a lot of question marks in the 'Risk of bias' tables.

Potential biases in the review process

Several studies included participants with impetigo next to participants with other conditions, but they did not report results of those with impetigo separately. However, as the number of participants with impetigo was often small in these studies, we do not expect that our conclusions would be different.

Three authors on this review are authors of one included trial (Sander Koning, Lisette WA van Suijlekom-Smit, Johannes C van der Wouden; Koning 2003), Sander Koning and Johannes C van der Wouden were also involved in a second trial (Koning 2008) which was initiated by the manufacturer of the drug. These authors were not involved in the assessment of the risk of bias for both studies.

Agreements and disagreements with other studies or reviews

Topical mupirocin and fusidic acid can be considered as effective as, or more effective than, oral antibiotics, and these topical agents have fewer side-effects. This finding is in sharp contrast to the previously held view that oral treatment is superior to topical treatment (Baltimore 1985; Tack 1998). Other topical antibiotics, excluding retapamulin, were generally inferior to mupirocin, fusidic acid, and oral antibiotics. The study by Vainer is an exception: no difference was seen between tetracycline/bacitracin cream, neomycin/bacitracin cream, and fusidic acid (Vainer 1986). Fusidic acid, mupirocin, and retapamulin are the only topical antibiotics that have been compared to placebo (and shown to be more effective).

For the results of the study comparing topical fusidic acid to retapamulin (Oranje 2007), the P value computed by Review Manager (RevMan) differs from the study report (0.07 in RevMan vs 0.062 in the study report) due to different methods (94.8% vs 90.1% cure, favouring retapamulin).

None of the studies reported cases of acute (post-streptococcal) glomerulonephritis. This complication has always been an important rationale for oral antibiotic treatment. This reported absence of glomerulonephritis may reflect the reduced importance of streptococci in impetigo. It should be noted that study sizes are small and glomerulonephritis is rare.

Several of the interventions used for impetigo have also been applied in other situations where *Staphylococcus aureus*, the main bacterium causing impetigo, plays a role. Here we review some of these, as reported in recently published Cochrane reviews. The effect of mupirocin ointment for preventing *S. aureus* infections in nasal carriers was superior to that of placebo or no treatment (van Rijen 2008). Birnie 2008 assessed interventions to reduce *S. aureus* in the management of atopic eczema, but the review did not find clear evidence of benefit for any of these. A review of the treatment of bacteraemia due to *S. aureus* is under way (Cheng 2009), as is a review of antibiotics for *S. aureus* pneumonia in adults (Shankar 2007). Mastitis in breastfeeding women is also caused by *S. aureus.* A recent Cochrane review found insufficient evidence to confirm or refute the effectiveness of antibiotic therapy (Jahanfar 2009).

AUTHORS' CONCLUSIONS

Implications for practice

Implications for topical disinfectants in clinical practice

There is a lack of evidence from RCTs for the value of disinfecting measures in the treatment of impetigo, as a sole or supplementary treatment.

Implications for topical antibiotics in clinical practice

There is good evidence that the topical antibiotics mupirocin and fusidic acid are equal to, or possibly more effective than, oral treatment for people with limited disease. Fusidic acid, mupirocin, and retapamulin are probably equally effective; other topical antibiotics seem less effective. In general, oral antibiotics have more side-effects than topical antibiotics, especially gastrointestinal side-effects.

Implications for use of systemic antibiotics in clinical practice

What is stated in the previous paragraph regarding the comparison with topical antibiotics is equally relevant here. The only oral antibiotic that has been compared to placebo is penicillin, and this was in an old study (Ruby 1973): no difference was found, and the confidence interval was large. Based on the available evidence on efficacy, no clear preference can be given for B-lactamase resistant narrow-spectrum penicillins such as cloxacillin, dicloxacillin and flucloxacillin, or for broad spectrum penicillins such as ampicillin, amoxicillin with clavulanic acid, cephalosporins or macrolides.

General considerations regarding the choice of antibiotics

Other criteria, such as price, (unnecessary) broadness of spectrum, and wish to reserve a particular antibiotic for specific conditions, can be decisive. Resistance rates against erythromycin seem to be rising. In general, oral antibiotics have more side-effects, especially gastrointestinal ones. There is insufficient evidence to say whether oral antibiotics are better than topicals for more serious and extensive forms of impetigo. From a practical standpoint, oral antibiotics might be an easier option for people with very extensive impetigo.

Implications for research

Trials should be powered to compare treatments for a specific disease entity, rather than the effectiveness of a specific antibiotic

on a variety of (skin) infections, as treatment may impact differently on separate subtypes of skin and soft tissue infections. As seen in this review, trials that study one treatment for several diseases often show inconclusive results for specific diagnoses. Future research on impetigo should make a careful power calculation as most included studies included too few participants with impetigo to meaningfully assess differences in treatment effect.

Establishing the natural course of impetigo without any form of antibiotic treatment would be useful. However, although impetigo can be considered a minor ailment, studies with a non-intervention arm seem ethically impracticable. Comparator treatments may include the best identified options for non-antibiotic management.

The relative absence of data on the efficacy of topical disinfectants is a research gap that needs to be filled. These agents may not contribute to antibiotic resistance, and they are cheap. This research may be of particular importance for developing countries.

Preferably, a trial on impetigo should:

- not include participants with a variety of skin diseases and soft tissue infections. If it does, results should be presented separately by diagnosis;
- focus on either bullous or non-bullous impetigo and on either primary or secondary impetigo;
- report resistance rates of causative bacteria against the studied antibiotic and against reference antibiotics such as erythromycin, mupirocin and/or fusidic acid, at baseline and at follow-up;
- use clear and objective outcome measures for cure and improvement of impetigo, instead of subjective judgements such as 'improved', 'satisfactory', and 'good response'. Key elements defining clinical cure could be absence of crusts, dryness, intactness, and absence of redness of skin. A parameter of improvement could be 'size of affected surface'. Choosing 'standard' follow-up periods, e.g. 7, 14, or 21 days, will facilitate the comparison of studies; and
- include a placebo group, or at least a 'gold standard' reference group. For topical treatments, mupirocin or fusidic acid could be considered 'gold standard'.

As part of the issue of antibiotic resistance, impetigo studies that establish the contribution of the studied treatment to the development of bacterial resistance are desirable.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Arata 1989a

Methods	Time NR; Japan; range of infections (impetigo 13/265)
Participants	• Age 15 to 82 years • M/F 150/115 (all participants) • Mainly *S.aureus*
Interventions	A: cefdinir 100 mg, 3 td B: cefaclor 250 mg, 3 td
Outcomes	**Outcomes of the trial**

Arata 1989a *(Continued)*

	1) 10 days, excellent/good/poor
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available in the abstract.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available in the abstract.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "....double-blind." Comment: There was unclear blinding of the outcome assessor and caregiver. The participant was probably blinded (see also Figure 2). The test drug packages also included placebo capsules.
Incomplete outcome data (attrition bias) All outcomes	Low risk	35/300 participants were omitted in the analysis: 16/147 in the cefdinir group (8 due to no or delayed visit to hospital, others for several reasons), 19/153 in the cefaclor group (8 due to no or delayed visit to hospital, others for several reasons) (see table 2).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance.
Randomised?	Unclear risk	Insufficient information was available in the abstract.
Were both inclusion and exclusion criteria specified?	Unclear risk	Insufficient information was available in the abstract.

Arata 1989b

Methods	Time NR; Japan; range of skin infections (including impetigo 18/259)
Participants	• All ages • M/F 162/97 • Mainly *S.aureus* (data for all participants)
Interventions	A: lomefloxacin 200 mg, 3 td B: norfloxacin 200 mg, 3 td
Outcomes	**Outcomes of the trial** 1) 7 days, cured/improved
Notes	-

Risk of bias

Arata 1989b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available in the abstract.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "...a double-blind clinical trial." It was unclear who was blinded (and how). The outcome assessor and caregiver were probably not blinded. The participant was probably blinded (see Figure 1 Dosing schedule).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	33/291 participants were omitted in the analysis: 15/147 in the NY-198 group, 17/144 in the norfloxacin group. There was insufficient information in the abstract and figures.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance.
Randomised?	Low risk	Quote: "...were randomly allocated to one of the two drugs."
Were both inclusion and exclusion criteria specified?	Unclear risk	Inclusion (quote): "...skin and soft tissue infections, patients > 15 years". There was no exclusion criteria.

Arredondo 1987

Methods	Time NR; Mexico city, Mexico; range of skin infections (including impetigo 55/61)
Participants	• Average age 7 years • M/F 30/31 • *S.aureus* 67%
Interventions	A: mupirocin ointment 2%, 3 td, 5 to 10 days B: dicloxacillin 250 mg, 4 td, 5 to 10 days
Outcomes	**Outcomes of the trial** 1) 10 days, cure
Notes	Open trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	This was not mentioned in the article.

Arredondo 1987 *(Continued)*

Blinding (performance bias and detection bias) patient	High risk	Quote: "In an open trial..." Participants received capsules or ointment. Neither the participant, caregiver, nor outcome assessor were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/61 participants were omitted in the analysis: 2/29 in the mupirocin group, 1/32 in the dicloxacillin group. Reasons for being non-evaluable for clinical outcome were not specified (but this was a small %).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	High risk	Baseline imbalance: more severe impetigo in the mupirocin group (9/32 vs 3/29, Table 1). There was no data on compliance.
Randomised?	Low risk	Quote: "After obtaining informed consent, patients were randomly divided into two treatment groups."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...pediatric patients with skin infections of sufficient severity to require treatment with a antibiotic." Quote: "Patients who...were excluded from the trial."

Barton 1987

Methods	June to August 1986; Missouri, USA; outpatients; only impetigo
Participants	• Children (age NR) • M/F 29/32 • *S.aureus* 35/65, *Streptococcus* 2/65, both: 30% PE
Interventions	A: penicillin V 50 mg/kg/day in 4 dd, 10 ds B: erythromycin 40 mg/kg/day in 4 dd, 10 ds
Outcomes	**Outcomes of the trial** 1) 7 days, failure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available about sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "The patients were assigned to receive either erythromycin or penicillin in a random, double-blind fashion by a pharmacist." Comment: Participants and investigators enrolling participants could not foresee assignment.
Blinding (performance bias and detection bias) patient	Unclear risk	See above - it was not specified how this was done. It is unclear whether the caregiver, participant, or outcome assessor was blinded.

Barton 1987 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	42/71 participants were omitted in the analysis - reasons and numbers were not specified for each group (6 due to negative culture, 21 not evaluable for effectiveness (not further specified), 6 due to no ascertained compliance, 3 due to no growth of *S. aureus* alone, 6 with*S. aureus* alone but not available for follow-up). 14 were left for analysis in the erythromycin group and 15 in the penicillin group.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Compliance and baseline comparability was unclear.
Randomised?	Low risk	Quote: "The patients were assigned to receive either erythromycin or penicillin in a random, double-blind fashion by a pharmacist."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "All patients examined in the outpatient department between June and August 1986 with primarily non bullous impetigo were asked to participate in the study if they were not receiving antibiotics at the time of being seen at CGH, had not taken antibiotics during the preceding week..."

Barton 1988

Methods	June to August 1987; Missouri, USA; outpatients; only impetigo
Participants	• 2 months to 16 years • M/F 55/45 • *S. aureus* 46/100, *S. pyogenes* 9/100, both 25/199 PE
Interventions	A: erythromycin 40 mg/kg/day in 4 dd, 10 ds B: dicloxacillin 25 mg/kg /day in 4 dd, 10 ds
Outcomes	**Outcomes of the trial** 1) 5 to 7 days, cure + improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Low risk	Quote: "Participants were randomly assigned in a double-blind manner by the hospital pharmacist to receive..." Hence, participants and investigators enrolling participants could not foresee assignment.
Blinding (performance bias and detection bias) patient	Unclear risk	See above - not specified how and who was blinded.

Barton 1988 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	41/100 participants were omitted in analysis - not specified for each group (12/100 were lost to follow up, but not stated from which group). 29 were left in the erythromycin group and 30 left in the dicloxacillin group.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Group assignment of non-compliant participants was unclear.
Randomised?	Low risk	Quote: "Participants were randomly assigned in a double-blind manner by the hospital pharmacist to receive..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "During the months of June, July and August, 1987, 100 children with impetigo, from whom informed consent was obtained, were consecutively enrolled in the study." Quote: "Exclusion criteria included..."

Barton 1989

Methods	June to August 1988; Missouri, USA; outpatients; only impetigo
Participants	• 3 months to 16 years • M/F 49/48 • *S. aureus* 80% PNE
Interventions	A: erythromycin 40 mg/kg/day in 3 dd, 7 days B: mupirocin ointment 2%, 3 td, 7 days
Outcomes	**Outcomes of the trial** 1) 4 to 7 days, cured + improved
Notes	14% bullous

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	This was not mentioned in the article.
Blinding (performance bias and detection bias) patient	High risk	Participant and caregiver were not blinded because they received either capsules or ointment. It is not mentioned in the article whether the outcome assessor was blinded (probably not, because the caregiver and participant were not blinded)
Incomplete outcome data (attrition bias) All outcomes	Low risk	1(/97) participant was omitted in the analysis, specified: 1/48 in the erythromycin group (lost to follow up), 0/49 in the mupirocin group.

Barton 1989 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Compliance was not reported.
Randomised?	Low risk	Quote: "Participants were randomly assigned to receive either..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Children over 6 weeks of age with a clinical diagnosis of impetigo were invited to participate in the study. Exclusion criteria included..."

Bass 1997

Methods	Time NR; Honolulu, Hawaii; hospital outpatients; only impetigo
Participants	• Average age 3.8 years • Sex NR • *S. aureus* 41/48 PNE
Interventions	3 arms: A: cephalexin 50 mg/kg/day in 3 dd + placebo ointment, 10 days B: mupirocin ointment 2%, 3 td + liquid oral placebo C: bacitracin ointment 500 units/g, 3 td + liquid oral placebo
Outcomes	**Outcomes of the trial** 1) 8 to 10 days, cure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...clinical pharmacist assigned them by a table of random numbers to one of the three treatment groups".
Allocation concealment (selection bias)	Low risk	See above and the quote: "The clinician, patients and their parents were not aware of which of the three treatment regimens they were assigned." Comment: Central allocation - participants and investigators enrolling participants could not foresee assignment.
Blinding (performance bias and detection bias) patient	Low risk	Quote: "The clinician, patients and their parents were not aware of which of the three treatment regimens they were assigned." Comment: The outcome assessor, participant, and caregiver were all blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	6/32 participants were omitted in the analysis: 0/10 in the cephalexin group, 5/12 in the mupirocin group, 1/10 in the bacitracin group (missing Imbalance for missing data).
Selective reporting (reporting bias)	Unclear risk	This was unclear.

Bass 1997 *(Continued)*

Other bias	Unclear risk	There was a baseline imbalance for size and type of lesion. Compliance was assessed in only 17 participants.
Randomised?	Low risk	Quote: "...clinical pharmacist assigned them by a table of random numbers to one of the three treatment groups."
Were both inclusion and exclusion criteria specified?	Low risk	Quoted from the referred article Demidovich: "Children presenting with impetigo to our clinic were eligible for the study. Exclusion criteria were..."

Beitner 1996

Methods	December 1992 to November 1994; 25 centres, Sweden; outpatients; range of skin infections (impetigo 60/327)
Participants	• Age range 3 to 80 years • *S. aureus* 86% of 327, *Streptococcus* 14% of 327 • Included only participants with bacteria sensitive to both drugs PE
Interventions	A: cefadroxil 40 mg/kg/day, 10 days B: flucloxacillin tablets 750 mg, 2 td, or susp 30 to 50 mg/kg/day in 2 to 3 dd, 10 days
Outcomes	**Outcomes of the trial** 1) 10 to 12 days, cure/improved/failed
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	The method of concealment was not described.
Blinding (performance bias and detection bias) patient	High risk	Quote: "...single blinded." Quote: "Statistical analysis was performed blinded." Comment: The participant, outcome assessor, and caregiver were probably not blinded because participants in both groups did not receive the same administrations of study drugs daily.
Incomplete outcome data (attrition bias) All outcomes	High risk	334/661 participants were missing mainly due to a lack of a bacterial culture sensitive to both drugs, and 351/661 were omitted from the primary analysis. 33 impetigo participants were included in the primary analysis. Exact reasons for not being evaluable and group assignment were not reported. 19/661 were omitted in the "ITT-analysis".
Selective reporting (reporting bias)	Unclear risk	This was unclear.

Beitner 1996 *(Continued)*

Other bias	Unclear risk	Quote: "The randomization produced two comparable groups of patients with no differences in known prognostic factors." Comment: There was no compliance data.
Randomised?	Low risk	Quote: "In this prospective single-blind comparative and randomized multicentre trial..."
Were both inclusion and exclusion criteria specified?	Low risk	Table 1: Inclusion and exclusion criteria for the subjects participating in the study.

Blaszcyk 1998

Methods	Period NR; multicentre; Europe, Latin America, Asia; range of skin infections (impetigo 42/539)
Participants	• 16 to 70 years (all participants) PNE
Interventions	A: clindamycin caps 150 mg, 4 td B: clindamycin caps 300 mg, 2 td C: dicloxacillin caps 250 mg, 4 td
Outcomes	**Outcomes of the trial** 1) 7 days, cure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Drug supplies were masked." Comment: Insufficient information was available.
Blinding (performance bias and detection bias) patient	Low risk	Quote: "Drug supplies were masked." Quote: "Patients in all groups received four administrations of study drugs daily." Comment: The outcome assessor, participant, and caregiver were probably all blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	48/588 were omitted in the analysis: 16/196 in the clindamycin caps 150 mg group, 19/198 in the clindamycin caps 300 mg group, 20/194 in the dicloxacillin caps group. Proportions of participants who did not complete the study medication and reasons were ˜ similar (table II). There were not only impetigo participants.
Selective reporting (reporting bias)	Unclear risk	This was unclear.

Blaszcyk 1998 *(Continued)*

Other bias	Unclear risk	Compliance data was provided (table II) and well-balanced. The distribution of baseline characteristics was not provided.
Randomised?	Low risk	Quote: "This prospective, double mask, randomized study..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Patients were selected based on..." Quote: "Patients were ineligible if..."

Britton 1990

Methods	October 1988 to October 1989; Portsmouth, Virginia, USA; outpatients; only impetigo
Participants	• 2 months to 12 years • M/F 27/17 • *S. aureus* 26/48 PNE
Interventions	A: erythromycin 40 mg/kg/day in 4 dd + placebo cream B: mupirocin ointment 2%, 3 td + placebo susp
Outcomes	**Outcomes of the trial** 1) 10 days, cured + improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a random numbers table, the hospital pharmacist randomly assigned each patient to one of the groups."
Allocation concealment (selection bias)	Low risk	Quote: "Using a random numbers table, the hospital pharmacist randomly assigned each patient to one of the groups." Comment: central allocation - pharmacy-controlled.
Blinding (performance bias and detection bias) patient	Low risk	Quote: "The child group assignment was not known to parents or investigators." Quote: "...assigned each patient to one of two groups: orally administered erythromycin plus topically applied placebo (erythromycin group) or orally administered placebo plus topically applied mupirocin (mupirocin group)." Comment: The outcome assessor, participant, and caregiver were probably all blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/54 participants were omitted in the analysis: 2/24 in the mupirocin group, 4/30 in the erythromycin group. Participants not completing the study were left out of the analysis. Reasons for not completing the study were not specified for each group. 3 were lost to follow up, 2 dropped out when misdiagnosis was suspected, and 1 was removed because of *S. pyogenes* pharyngitis. < 20% withdrawals and numbers were balanced.

Britton 1990 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	High risk	Baseline characteristics were imbalanced (sex, severity), and compliance was also skewed.
Randomised?	Low risk	Quote: "Using a random numbers table, the hospital pharmacist randomly assigned each patient to one of the groups."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Children aged 12 years and younger with the clinical diagnosis of impetigo..." Quote: "We excluded..."

Bucko 2002a

Methods	Unlear, around 2000; US, multicentre; ambulatory setting; range of skin infections (including impetigo 58/857)
Participants	• 12 to 93 years • M/F 427/430 • *S.aureus* 525/1685, *S.pyogenes* 53/1685 (including Bucko 2002b) PNE
Interventions	A: cefditoren 200 mg, 2 td, 10 days B: cefditoren 400 mg, 2 td, 10 days C: cefuroxime 250 mg, 2 td, 10 days
Outcomes	**Outcomes of the trial** 1) 7 to 14 days, cured or improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was not reported.
Allocation concealment (selection bias)	Low risk	Quote: "Study-drug containers were dispensed in numeric sequence at each investigative site as patients were enrolled to ensure random assignment."
Blinding (performance bias and detection bias) patient	Low risk	Quote: "...double-blind, double-dummy..." Quote: "Patients' evaluability and outcomes were assessed under blinded conditions". The outcome assessor, caregiver, and participant were all blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For only impetigo: 2/58 missing impetigo participants in total - 0/19 in the cefditoren 200 mg group, 2/21 in the cefditoren 400 mg group, 0/18 in the cefuroxime 250 mg group. Reasons for missing participants were not specified (but a small % were non-evaluable)

Bucko 2002a *(Continued)*

Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no compliance data and no baseline imbalance.
Randomised?	Low risk	Quote: "Patients were randomized."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Eligible patients included..." Quote: "Study exclusion criteria included..."

Bucko 2002b

Methods	Unclear, around 2000; US; multicentre; ambulatory setting; range of skin infections (including impetigo 74/828)
Participants	• 12 to 95 years • M/F 428/400 • *S.aureus* 525/1685, *S.pyogenes* 53/1685 (including Bucko 2002a) PNE
Interventions	A: Cefditoren 200 mg, 2 td, 10 days B: Cefditoren 400 mg, 2 td, 10 days C: Cefadroxil 500 mg, 2 td, 10 days
Outcomes	**Outcomes of the trial** 1) 7 to 14 days, cured or improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was not reported.
Allocation concealment (selection bias)	Low risk	Quote: "Study-drug containers were dispensed in numeric sequence at each investigative site as patients were enrolled to ensure random assignment."
Blinding (performance bias and detection bias) patient	Low risk	Quote: "...double-blind, double-dummy..." Quote: "Patients' evaluability and outcomes were assessed under blinded conditions". Comment: The outcome assessor, caregiver, and participant were all blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For only impetigo: 4/74 missing participants - 1/27 in the cefditoren 200 mg group, 0/25 in the cefditoren 400 mg group, 3/22 in the cefadroxil 500 mg group. Reasons for missing participants were not specified (but a small % were non-evaluable)

Bucko 2002b *(Continued)*

Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no compliance data and no baseline imbalance.
Randomised?	Low risk	Quote: "Patients were randomized..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Eligible patients included..." Quote: "Study exclusion criteria included..."

Christensen 1994

Methods	Time NR; Sweden, Germany, UK; Outpatients (Germany) and GP (UK), both (Sweden); only impetigo
Participants	• 3 + years • M/F 131/125 • *S.aureus* 199/256, *S.pyogenes* 21/256, both 36/256 PE
Interventions	A: hydrogen peroxide cream 1% (Microcid), 2 to 3 td, max 21 days B: fusidic acid cream gel 2%, 2 to 3 td, max 21 days
Outcomes	**Outcomes of the trial** 1) evaluation time NR, cure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomized (in blocks of four)." The process for selecting the blocks was not specified.
Allocation concealment (selection bias)	Unclear risk	Quote: "The tubes were put into identical paper boxes, to keep the trials blind." Comment: Insufficient information was available. The tubes may have been different.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "The tubes were put into identical paper boxes, to keep the trials blind." There was incomplete blinding - participants were probably not blinded (see above), and blinding with regard to the outcome assessor and caregiver is unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	135/391 participants were omitted in the analysis because they were culture negative (not specified per group); 11/156 participants in the M-group and 3/156 in the F-group were withdrawn due to deterioration of their impetigo (statistically significant), 3/156 in the F-group and 0/156 in the M-group were withdrawn due to adverse events (irritation of the skin, burning, and blistering). All participants fulfilling the prespecified requirement of bacteriologically-verified impetigo were analysed.

Christensen 1994 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were no data on baseline comparability and compliance.
Randomised?	Low risk	Quote: "...randomized (in blocks of four)."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...were included" Quote: "Patients were not allowed... prior to start of study..."

Ciftci 2002

Methods	1999; Turkey; hospital outpatient department; only impetigo
Participants	• Age 10 to 132 months • M/F 32/16 • *S. aureus* around 70%
Interventions	A: topical mupirocin 2% 3td for 10 days B: topical terbinafine 1% 3td for 10 days
Outcomes	**Outcomes of the trial** 1) 10 days, cure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	High risk	Quote: "...mupirocin group was instructed to use Bactroban 2% ointment and terbinafine group was instructed to use Lamisil 1% cream topically three times daily for ten days". The outcome assessor, caregiver, and participant were not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	14/62 participants were not analysed: 6/31 were missing in the mupirocin group, 8/31 were missing in the terbinafine group. Quote: "At the end of the treatment, 25 participants in the mupirocin group and 23 participants in the terbinafine group were considered eligible" . > 20% missing.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	High risk	Quote: "The group had similar features except for the time from appearance of lesions to hospital admission." There was a mean of 5.44 in the mupirocin group versus 6.78 in the terbinafine group.

Ciftci 2002 *(Continued)*

Randomised?	Low risk	Quote: "...in a randomized fashion."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...were excluded." Quote: "....children, less than 12 years old, presenting with impetigo to..."

Claudy 2001

Methods	Time NR; France; ambulatory setting (dermatology outpatient departments); range of skin infections (including impetigo 53/334)
Participants	• All participants: age > 18 years • M/F 206/128 • *S aureus*: 162/334; *S pyogenes* 34/334
Interventions	A: oral fusidic acid 2 x 250 mg 2 td for 7.5 days B: oral pristinamycin 2 x 500 mg 2 td for 10 days
Outcomes	**Outcomes of the trial** 1) 11 days, cured and improved
Notes	Outcome data for impetigo participants was provided by the author (personal communication).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "Afin de garantir le double insu, chaque patient recevait le traitement dont 2.5 jours de placebo". [To ensure double blinding, each patient received a placebo for 2.5 days]. The participants were blinded, but blinding is unclear with regard to the caregiver and outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	313/334 participants were analysed (< 10% not in analysis). There is no data for impetigo participants.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were no compliance data and no baseline comparison.
Randomised?	Low risk	Quote: "Une etude multicentrique, prospective, randomisée..." [A randomised, prospective, multicentre study...]
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Tout patient ambulatoire, âgé de plus de 18 ans, avec une pyodermite superficielle nécessitant une antibiothérapie orale et ayant donné son consentement éclairé pouvait être inclus dans l'essai à condition de ne presenter aucun des critères d'exclusion suivants." [Most ambulatory participants,

Claudy 2001 *(Continued)*

	older than the 18 years old, with a superficial pyoderma requiring oral antibiotics and with given informed consent could be included in the study provided there were none of the following exclusion criteria present.]

Dagan 1989

Methods	May to October 1987; Negev region, Israel; outpatients; only impetigo
Participants	• 6 months to 9 years • Sex NR • *S. aureus* 37/51, *S. pyogenes* 14/51 PE
Interventions	A: amoxicillin trihydrate syrup 40 mg/kg/day, in 3 dd, 10 days B: amoxicillin/clavulanic acid syrup 40 + 10 mg/kg/day, in 3 dd, 10 days
Outcomes	**Outcomes of the trial** 1) 5 days, cure + improved
Notes	There was missing data from the first follow-up measurement for 4/26 participants in the amoxicillin trihydrate syrup group and 3/25 participants in the amoxicillin/clavulanic acid syrup group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "...in a double-blind fashion". It is unclear whether the outcome assessor, participant, or caregiver were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/52 (< 20%) participants were omitted in the analysis after 5 days.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	High risk	There was a baseline imbalance for lymphadenopathy > 20%. There were no compliance data.
Randomised?	Low risk	Quote: "After obtaining the cultures, patients were randomized to..."
Were both inclusion and exclusion criteria specified?	High risk	Quote: "We included..." Exclusion criteria was not mentioned.

Dagan 1992

Methods	July 1989 to October 1990; Negev region, Israel; outpatients; only impetigo (bullous and non-bullous)
Participants	• < 16 years • M/F 56/46 • *S. aureus* 90/102, streptococci 1/3 of participants PNE
Interventions	A: erythromycin susp 50 mg/kg/day 3 td + placebo ointment, 7 days B: mupirocin ointment 2% 3 td + oral placebo susp, 7 days
Outcomes	**Outcomes of the trial** 1) 7 days, failed
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Low risk	Quote: "The randomized code was prepared by Beecham Pharmaceutical and was not known to the investigators until after the raw data were tabulated."
Blinding (performance bias and detection bias) patient	Low risk	Quote: "The randomized code was prepared by Beecham Pharmaceutical and was not known to the investigators until after the raw data were tabulated." The erythromycin group received a placebo ointment and the mupirocin group received an oral placebo suspension. The outcome assessor, caregiver, and participant were probably all blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	13/102 participants were omitted in the analysis: 8/51 in the erythromycin group (1 due to side-effects, 7 due to refusal to continue treatment or to return for the follow-up visit), 5/51 missing in the mupirocin group (all due to refusal to continue treatment or to return for the follow-up visit).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were age and sex differences at baseline (table 1), although they were not significant. There were no compliance data.
Randomised?	Low risk	Quote: "...were randomized into two groups."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Infants... were enrolled." Quote: "Excluded groups were..."

Daniel 1991a

Methods	1987 to 1991; Belgium, France, FRG, Netherlands, Norway, UK; setting unclear; range of skin infections (including impetigo 69/308)
Participants	• 16 to 80 years

Daniel 1991a *(Continued)*

	• All participants: *S. aureus* 195/308, streptococci 59/308 PNE
Interventions	A: azithromycin 250 mg twice (day 1),once daily (day 2 to 5), 5 days B: erythromycin 500 mg 4 td, 7 days
Outcomes	**Outcomes of the trial** 1) 11 to 16 days, cured
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were allocated to treatment with azithromycin or erythromycin in a 1:1 ratio using a randomization list."
Allocation concealment (selection bias)	Unclear risk	See above - it is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	High risk	Participants in both groups did not receive the same administrations of study drugs daily. The outcome assessor was likely to also be the caregiver, so probably all 3 were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of impetigo participants not included in analysis was small and well-balanced (1 vs 2).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were no compliance data. Baseline characteristics were well-balanced.
Randomised?	Low risk	Quote: "Patients were allocated to treatment with azithromycin or erythromycin in a 1:1 ratio using a randomization list."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "In order to be included..." Quote: "Exclusion criteria were..."

Daniel 1991b

Methods	1987 to 1989; Belgium, Germany, Ireland, UK; setting unclear; range of skin infections (including impetigo 17/323)
Participants	• Adults 17 to 90 years • All participants: *S aureus* 158/323, streptococci 41/323 PNE
Interventions	A: azithromycin 250 mg twice (day 1),once daily (day 2 to 5), 5 days B: cloxacillin 500 mg, 4 td, 7 days
Outcomes	**Outcomes of the trial**

Daniel 1991b *(Continued)*

	1) 11 to 16 days, cured/improved/failed
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a presupplied randomization list patients were allocated to receive azithromycin or cloxacillin in the ratio of 2:1."
Allocation concealment (selection bias)	Unclear risk	See above - it is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	High risk	Participants in both groups did not receive the same administrations of study drugs daily. The outcome assessor, caregiver, and participant were probably not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 impetigo participant was not in the analysis.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were no compliance data. Baseline characteristics were comparable.
Randomised?	Low risk	Quote: "Using a presupplied randomization list patients were allocated to receive azithromycin or cloxacillin in the ratio of 2:1."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "In order to be included..." Quote: "Exclusion criteria were..."

Demidovich 1990

Methods	Time NR; Honolulu, Hawaii; outpatients; only impetigo
Participants	• 5 months to 15 years, average 3 years • *S. aureus* 45/73, GABHS 6/73, both 14/73 PNE
Interventions	A: penicillin V 40 to 50 mg/kg/day in 3 dd, 10 days B: cephalexin 40 to 50 mg/kg/day in 3 dd, 10 days C: erythromycin 30 to 40 mg/kg/day in 3 dd, 10 days
Outcomes	**Outcomes of the trial** 1) 8 to 10 days, failed
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Demidovich 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Low risk	Quote: "The pharmacist randomly assigned them to one of three treatment regimens." Central allocation - participants could not foresee assignment.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "Patients were reevaluated...by one of the authors, both of whom were blinded to the treatment each child was receiving." Comment: Participants were probably not blinded. The caregiver and outcome assessor were probably blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/75 participants were omitted in the analysis: 2 participants were lost to follow up (not further specified).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Quote: "There was not a significant difference in disease severity among treatment groups." Compliance in both groups was comparable, but low.
Randomised?	Low risk	Quote: "The pharmacist randomly assigned them to one of three treatment regimens."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Children presenting with impetigo to our pediatric clinic were eligible for the study. Exclusion criteria were..."

Dillon 1983

Methods	1980 summer/fall; Alabama, USA; outpatients; only impetigo (bullous impetigo 57/70)
Participants	• Average age 3.2 years • MF 41/37 • *S. aureus*: 64/70 PNE
Interventions	A: cephalexin 50 mg/kg/day in 2 dd (> 20 kg: 500 mg 2 td) B: dicloxacillin 15 mg/kg/day in 4 dd (> 40 kg: 125 mg 4 td)
Outcomes	**Outcomes of the trial** 1) Prompt cure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned, according to a standard table, to receive..." (Referring to a standard table.)

Dillon 1983 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	See above - it is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	High risk	Participants in both groups did not receive the same administrations of study drugs daily. The outcome assessor, caregiver, and participant were probably not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/78 participants were omitted in the analysis: 5 vs 3 participants failed to return or, with a negative culture, were not included in the analysis (< 20% and balanced).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Quote: "Preference was given to patients with skin infections typical of staphylococcal bullous impetigo." Comment: Furthermore, there were no baseline differences, and compliance was not reported.
Randomised?	Low risk	Quote: "Patients were randomly assigned, according to a standard table, to receive..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "The criterion for enrolment was..." Quote: "...were excluded."

Dux 1986

Methods	Time NR; Toronto, Canada; setting unclear; range of skin infections (including impetigo 36/149)
Participants	• Average age 22 years • M/F 81/68 • Bacterial culture results unclear PNE
Interventions	A: mupirocin ointment 2%, 3 td, 7 days B: erythromycin 250 mg, 4 td, 7 days C: cloxacillin 250 mg, 4 td, 7 days
Outcomes	**Outcomes of the trial** 1) 7 days, cure/improved/failure. Clocacillin: no participants with impetigo allocated
Notes	2 cases of secondary impetigo, both in the mupirocin group, were excluded from the results presented here.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process was available, and there was unexpected distribution (78 vs 50 vs 20).

Dux 1986 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "...were randomized into two treatment groups by each investigator." Comment: It is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "...single-blind". Comment: It is not clear who was blinded and how this was done. Also, participants in both groups did not receive the same administrations of study drugs daily. Participants were probably not blinded. The blinding of outcome assessor and caregiver is unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 (/149) participant was omitted in the analysis: 1/79 in the mupirocin group due to an infected cyst (not included in analysis), 0/50 in the erythromycin group, 0/20 in the cloxacillin group.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Compliance was not reported. There was a large age difference between groups (mean 22 vs 31 years), unknown for impetigo participants.
Randomised?	Low risk	Quote: "In each section of the study, patients with primary or secondary skin infections were randomized into two treatment groups."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Patients with primary and secondary skin infections that were severe enough were included in three parallel-study groups." Quote: "Patient who did not..."

Eells 1986

Methods	October to November 1983; Puerto Rico; outpatients; only impetigo
Participants	• 7 months to 13 years • M/F 13/25 • Mainly *S.aureus* PE
Interventions	A: mupirocin ointment 2%, 3 td, 7 to 9 days B: vehicle control, 3 td, 7 to 9 days
Outcomes	**Outcomes of the trial** 1) 8 days, cure/improved/failure 1 participant with ecthyma was excluded in each group.
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Eells 1986 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized between the two treatment groups by a computer-generated set of random numbers in blocks of five per group."
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Low risk	Quote: "...double-blind, vehicle-controlled." Also, participants in both groups received the same administrations of study drugs daily. The outcome assessor, caregiver, and participant were probably all blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	14/52 participants were omitted in the analysis: 8/26 in the mupirocin group (5 were "unavailable for follow-up", 3 for several reasons (specified)), 6/26 in the vehicle group (2 were "unavailable for follow-up", 3 for several reasons (specified)). There were more than 20% withdrawals and dropouts.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance. Compliance was not reported.
Randomised?	Low risk	Quote: "Patients were randomized between the two treatment groups by a computer-generated set of random numbers in blocks of five per group."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...were admitted to the study." Quote: "Patients were excluded if..."

Esterly 1991

Methods	Time NR; Milwaukee, Wisconsin, USA; outpatients; only impetigo
Participants	• 3 months to 14 years, average 4.3 years • *S.aureus* 33%; GABHS 12%; both 41% • Exclusions: NR
Interventions	A: mupirocin (dose NR) B: erythromycin (dose NR)
Outcomes	**Outcomes of the trial** 1) Time of evaluation NR, failure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	It is unclear whether participants and investigators enrolling participants could foresee assignment.

Esterly 1991 *(Continued)*

Blinding (performance bias and detection bias) patient	High risk	Oral versus topical treatment. The outcome assessor, caregiver, and participant were probably not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	9/48 participants were omitted in the analysis: 4/25 in the mupirocin group (3 due to "fail to return for follow-up", 1 reason not mentioned), 5/23 in the erythromycin group (3 due to "fail to return for follow-up", 2 reasons not mentioned).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were no baseline characteristics per group. There were no compliance data.
Randomised?	Low risk	Quote: "...randomized."
Were both inclusion and exclusion criteria specified?	High risk	This was not mentioned in the article.

Farah 1967

Methods	Time NR; Lebanon; outpatients; probably all impetigo ('superificial pyogenic skin infection')
Participants	• 21 days to 60 years of age • M/F unknown • *S. aureus* 61%, *S. pyogenes* 30%
Interventions	A: gentamycin cream 1% 3 td, duration unknown B: neomycin ointment 0.5% 3 td, duration unknown
Outcomes	**Outcomes of the trial** 1) Cured, improved after 7 days
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was provided.
Allocation concealment (selection bias)	Unclear risk	This was not reported.
Blinding (performance bias and detection bias) patient	Unclear risk	This was not reported.
Incomplete outcome data (attrition bias)	Unclear risk	11/139 participants were lost to follow up (it was not stated in which group).

Farah 1967 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was an unexplained imbalance of group size (88 vs. 44). There were no compliance data. There was no baseline comparison.
Randomised?	Low risk	Quote: "The persons included in this study were divided into two groups at random."
Were both inclusion and exclusion criteria specified?	High risk	Inclusion and exclusion criteria was not specified.

Faye 2007

Methods	2002 to 2003; Mali; hospital outpatients; only impetigo
Participants	• Inclusion > 1 year of age • Mean age 8.5 years • M/F 74/58 • No bacteriological investigation
Interventions	A: oral amoxicillin 50 mg/kg/day + topical 10% povidone iodine for 7 days B: oral erythromycin 30 mg/kg/day + topical 10% povidone iodine for 7 days
Outcomes	**Outcomes of the trial** 1) Proportion cured + improved after 7 days
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...using a table of random numbers". Comment: This was an adequate method.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	High risk	Quote: "....an open randomized trial." Quote: "Patients and investigators were not blinded." The outcome assessor, participant, and caregiver were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/132 participants were not analysed: 2/66 in the amoxicillin group (2 lost to follow up on the 7th day), 1/66 in the erythromycin group (1 lost to follow up on the 7th day).
Selective reporting (reporting bias)	Unclear risk	This was unclear.

Faye 2007 *(Continued)*

Other bias	Unclear risk	There was no baseline comparison. There were no compliance data.
Randomised?	Low risk	Quote: "...an open randomized trial."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Patients aged more than 1 year old... were considered for inclusion." Quote: "The following cases were excluded..."

Fujita 1984

Methods	Time NR; Japan; outpatients; range of skin infections (including impetigo 10/204)
Participants	• Age 16 to 84 years • M/F 120/84 (all participants)
Interventions	A: enoxacin 500 mg 3 td B: cephalexin 500 mg 2 td (double dummy)
Outcomes	**Outcomes of the trial** 1) After .... cured/improved
Notes	Secondary impetigo- it only says impetigo above

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was not mentioned in the abstract.
Allocation concealment (selection bias)	Unclear risk	This was not mentioned in the abstract.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "...a double-blind." They used placebo capsules (see Figure 1 Dosage schedule). Participants were probably blinded. It is not clear how, and if, the caregiver and outcome assessor were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	22/226 participants were omitted in the analysis: 14/115 in the enoxacin group (2 due to exclusion (1 overlap administration and 1 antibiotics before treatment), 12 dropped out (11 shortage of duration, 1 no successive visit)), 8/111 in the cephalexin group (all dropped out (7 shortage of duration, 1 no successive visit). < 20% but not specified for impetigo participants.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance (table 4), and compliance was not reported.
Randomised?	Unclear risk	This was not mentioned in the abstract.
Were both inclusion and exclusion criteria specified?	Unclear risk	This was not mentioned in the abstract.

Gilbert 1989

Methods	Time NR; Quebec, Canada; outpatients; range of skin infections (including impetigo 19/70)
Participants	• Age NR • *S. aureus* 41/70; Streptococci 22/70 (all participants) PE
Interventions	A: mupirocin ointment 2%, 3 td, 7 days B: fusidic acid cream 2%, 3 td, 7 days
Outcomes	**Outcomes of the trial** 1) 7 days, cure/improved/failure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Unclear risk	The abstract reported the study was double-blind, but it is not explained in the article. There is unclear blinding of the outcome assessor, caregiver, and participant.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 (/70) participant was omitted in the clinical analysis: 0/35 in the fusidic acid group, 1/35 in the mupirocin group. Participants were not examined if pre-treatment cultures were negative or if post-treatment evaluation was not possible.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance, and compliance was not reported.
Randomised?	Low risk	Quote: "Patients were randomly divided into two treatment groups."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Patients who... were excluded from the trial." Quote: "...in 70 patients who came to the dermatologic clinic with primary and secondary skin infections of sufficient severity to require antibiotic therapy."

Ginsburg 1978

Methods	Time NR; Dallas, Texas, USA; outpatients; only impetigo
Participants	• 8 months to 8 years, average 3.1 years • Sex NR • *S.aureus* 78%, GABHS 64%, both 50%

Ginsburg 1978 *(Continued)*

	Part excluded: unclear
Interventions	A: penicillin G 30 mg/kg/day in 4 dd, duration NR B: cefadroxil 45 mg/kg/day in 3 dd, duration NR
Outcomes	**Outcomes of the trial** 1) 8 days, cured + improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	It is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	High risk	Participants in both groups received different administrations of study drugs daily. The outcome assessor, caregiver, and participant were probably not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	21/71 participants were omitted in the analysis due to failure to return for both follow-up examinations. There were more than 20% withdrawals; this was not further specified for each group.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Quote: "Groups were comparable with regard to age, sex, race and extent of skin lesion." Compliance was unclear.
Randomised?	Low risk	Quote: "Infants and children with impetigo were assigned treatment randomly."
Were both inclusion and exclusion criteria specified?	High risk	Quote: "Infants and children with impetigo were assigned..." No exclusion criteria were specified.

Giordano 2006

Methods	2005; US; hospital outpatients; skin infections (including impetigo 16/391)
Participants	• All diagnoses: 13 to 93 years • M/F 206/185 • *S. aureus* 44%; *S. pyogenes* 2%
Interventions	A: oral cefdinir 300 mg 2 td 10 days B: cephalexin 200 mg 4 td 10 days
Outcomes	**Outcomes of the trial**

Giordano 2006 *(Continued)*

	1) Proportion cured + improved after 17 to 24 days
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomization schedule in a 1:1 ratio was used." Quote: "Study drug containers were dispensed in increasing numerical sequence at each investigative site."
Allocation concealment (selection bias)	Unclear risk	Quote: "To maintain investigator blinding, the study drug was dispensed by an unblinded third person who did not participate in the assessments of clinical response." Comment: It is not clear whether this person was involved in participant contacts.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "...investigator-blinded." Quote: "To maintain investigator blinding, the study drug was dispensed by an unblinded third person who did not participate in the assessments of clinical response. Furthermore, the participant was instructed not to disclose any details about the study drug (...) to the investigator." The outcome assessor and caregiver were blinded. The participants were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 0/16 missing impetigo participants: 0/4 in the cefdinir group, 0/12 in the cephalexin group. All 391 who took at least 1 dose of the study drug were analysed.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were no compliance data. There was no baseline comparison.
Randomised?	Low risk	Quote: "A computer-generated randomization schedule..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...were enrolled" Quote: "Study exclusion criteria included..."

Goldfarb 1988

Methods	Time NR; Cleveland, Ohio, USA; outpatients; only impetigo
Participants	• 5 months to 13 years, average 3.8 • M/F 31/31 • *S.aureus* 49/62, Streptococci 4/62, both 9/62 PE: NR
Interventions	A: mupirocin ointment 2%, 3 td, 8 days B: erythromycin 40 mg/kg/day in 4 dd, 8 days

Goldfarb 1988 *(Continued)*

Outcomes	**Outcomes of the trial** 1) 8 days, cured/failed
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	It is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	High risk	Topical versus oral treatment. The outcome assessor, caregiver, and participant were probably not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/62 participants were lost in total: 5/30 in the mupirocin group (all lost to follow up), 5/32 in the erythromycin group (all lost to follow up).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	The severity of impetigo was not compared between the 2 groups. There was a difference in age (range vs mean). Compliance was not reported.
Randomised?	Low risk	Quote: "Enrolled children were randomly assigned to groups that..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Children 3 months of age and older were seen at...were eligible for our study." Quote: "Children were excluded if..."

Gonzalez 1989

Methods	July to September 1980; Florida, USA; outpatients; only impetigo (bullous and non-bullous).
Participants	• 6 months to 12 years Participants were excluded if no *S. aureus was* present
Interventions	A: penicillin V potassium 50 mg/kg/day, in 4 dd, 10 days B: cloxacillin sodium 50 mg/kg/day, in 4 dd, 10 days
Outcomes	**Outcomes of the trial** 1) 10 days: cured + improved
Notes	-

Risk of bias

Gonzalez 1989 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Quote: "...on a randomized schedule at the following dosages". It is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "The clinical examiners were blinded to the antibiotic that the patients received until the study was concluded." Quote: "...double-blind schedule." It is not clear how patients were blinded, and the participant was likely to be influenced in the case of lack of blinding. The outcome assessor and caregiver were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	24/101 participants were lost due to no *S. aureus* growth, 10 were lost in failure to return to the clinic (reasons for not attending follow-up visit were not stated). The imbalance in participants was not evaluated.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline severity comparison between groups. Participant compliance data was computed and presented no significant alterations in therapeutic outcome.
Randomised?	Low risk	Quote: "...on a randomized schedule at the following dosages..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...could be enrolled on the study if the following criteria were met..." Quote: "There were no prior histories of allergic phenomena."

Gould 1984

Methods	Time NR; Edinburgh, UK; general practice; range of skin infections (including impetigo 39/107)
Participants	• Average age 18.7 (all participants) • *S. aureus* 90/129, streptococci 32/129 (all participants) PNE
Interventions	A: mupirocin ointment 2%, once daily, until cleared B: placebo cream, once daily, until cleared
Outcomes	**Outcomes of the trial** 1) Time of evaluation NR, cure/improved/failure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Gould 1984 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were allocated a trial number in the consecutive order of their entry in the study. The study was performed under double blind conditions. Medication appropriate to the trial number, either mupirocin or placebo ointment, was dispensed according to a pre-determined randomization which ensured that in each group of four patients, two received treatment with mupirocin and two with placebo ointment." The process for selecting the blocks was not specified.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "The study was performed under double-blind conditions." It is unclear whether, and how, the outcome assessor, caregiver, and participant were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14/107 participants were omitted in the analysis: 10/54 in the mupirocin group (they were classified as clinically unassessable, 7 did not return for final assessment (5 were traced later and found to have clinically improved), 3 developed other diseases requiring systemic treatment), 4/53 in the placebo group (3 did not return for final assessment (2 of whom were later found to have improved and one worsened and sought alternative treatment), 1 developed other disease requiring systemic treatment). < 20%, 3 vs 1 impetigo participant not evaluable.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Quote: "...well matched". There was no compliance data.
Randomised?	Low risk	Quote: "...according to a pre-determined randomization."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Patients with acute primary skin infections...who had not received topical or systemic antibiotics during the preceding 3 days were entered in the study."

Gratton 1987

Methods	Time NR; Montreal, Quebec, Canada; outpatients; range of skin infections (including impetigo 15/60)
Participants	• Age/sex NR • *S. aureus* approx 50% PE: NR
Interventions	A: mupirocin ointment 2%, 3 td, 7 days B: erythromycin 250 mg, 4 td, 7 days
Outcomes	**Outcomes of the trial** 1) 7 days, cure/improved/failure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Gratton 1987 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Quote: "...were randomly divided into two treatment groups." It is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	High risk	Topical versus oral treatment. The outcome assessor, caregiver, and participant were probably not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/60 participants were omitted in the analysis: 0/30 in the mupirocin group, 0/30 in the erythromycin group. 1 participant in the mupirocin group discontinued therapy due to intolerable side-effects. All impetigo participants were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline data. There were no compliance data.
Randomised?	Low risk	Quote: "...were randomly divided into two treatment groups."
Were both inclusion and exclusion criteria specified?	High risk	Quote: "Sixty patients with primary and secondary skin infections were randomly divided." No exclusion criteria was specified.

Hains 1989

Methods	Summer 1986; Birmingham, Alabama, US; outpatients child hospital; only impetigo
Participants	• 1 to 18 years • Sex NR • *S. aureus* 35%, GABHS 12%, both 54% PE: NR
Interventions	A: cefadroxil 30 mg/kg/day, max 1 g, in 1 dd, 10 days B: cephalexin 30 mg/kg/day, max 1 g, in 2 dd, 10 days
Outcomes	**Outcomes of the trial** 1) 14 days, cured
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.

Hains 1989 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to receive either..." It is unclear whether participants and investigators enrolling patients could foresee assignment.
Blinding (performance bias and detection bias) patient	High risk	Participants in both groups received different administrations of study drugs daily. The outcome assessor, caregiver, and participant were probably not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	13/101 participants were omitted in the analysis in total: 4/55 in the cefadroxil group (1 failed to keep all of the appointments, 3 participants failed to take medications as prescribed), 9/54 in the cephalexin group (3 with negative cultures, 4 failed to keep all of the appointments, 2 participants failed to take medications as prescribed). < 20% and reasons described.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was baseline data. Compliance was good in both groups.
Randomised?	Low risk	Quote: "Patients were randomly assigned to receive either..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...who had a clinical diagnosis of pyoderma were enrolled." Quote: "Children were excluded if..."

Ishii 1977

Methods	Summer 1976; Tokyo, Japan; hospital outpatient clinic; bullous impetigo
Participants	• 0 to 10 years • M/F 26/34 • No bacterial investigations • All participants evaluable
Interventions	A: topical Eksalbe simplex (ointment containing killed *escherichia*, *staphylococcus*, *streptococcus*, and *pseudomonas*) applied once daily under plaster or 3 times daily without plaster B: placebo
Outcomes	**Outcomes of the trial** 1) Cured/improved after 4 days
Notes	Data extraction and risk of bias assessment done by Testuri Matsumura.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This was not reported.
Allocation concealment (selection bias)	Low risk	Allocation was concealed (assessed by Tetsuru Matsumura).

Ishii 1977 *(Continued)*

Blinding (performance bias and detection bias) patient	Low risk	The participant, outcome assessor, and caregiver were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/40 participants were dropouts and excluded from the analysis.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were no compliance data.
Randomised?	Low risk	This trial was randomised (assessed by Tetsuru Matsumura).
Were both inclusion and exclusion criteria specified?	High risk	Exclusion criteria were not specified.

Jaffe 1985

Methods	Time NR; Cleveland, Ohio, USA; outpatients child clinic; range of skin infections (including impetigo 32/42)
Participants	• 6 months to 12 years, average 4.8 years • *S. aureus* 33/36, *S. pyogenes* 8/36 PNE
Interventions	A: amoxicillin/clavulanic (125/30) acid, dose equivalent to 20 mg amoxicillin/kg/day in 3 dd, 10 days B: cefaclor 20 mg/kg/day in 3 dd
Outcomes	**Outcomes of the trial** 1) 10 days, cured/failed
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Low risk	Quote: "Prescription were filled by the hospital pharmacist using double-blind labels." Personnel or participants could, probably, not foresee assignment.
Blinding (performance bias and detection bias) patient	Low risk	Quote: "Prescription were filled by the hospital pharmacist using double-blind labels." The outcome assessor, caregiver, and participant were probably all blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/43 participants were omitted in the analysis: 0/21 in the amoxicillin/clavulanic acid group, 0/22 in the cefaclor group.

Jaffe 1985 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Low risk	Quote: "The two treatment groups were generally comparable." Compliance was good in 75% of participants.
Randomised?	Low risk	Quote: "Children were randomly assigned to one of the two treatment regimens."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Children 6 months to...were eligible for inclusion in the study." Quote: "Exclusion criteria included..."

Jaffe 1986

Methods	Time NR; multicentre, Wessex, UK; general practice; range of skin infections (including impetigo 43/119)
Participants	• 2.5 years to 83 years, median 14 to 16 years • M/F 23/20 • *S. aureus* 16/34, *S. pyogenes* 5/34 PNE
Interventions	A: 1% hydrocortisone + 0.5% potassium hydroxyquinoline sulphate cream, 2 td, 14 days B: 1% hydrocortisone + 2% miconazole nitrate cream, 2 td, 14 days
Outcomes	**Outcomes of the trial** 7 days, cured/improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Quote: "The trial was double-blind, patients being allocated at random to receive..." Quote: "The randomization was balanced for each centre, with separate randomizations for each of the two indications." It is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	Low risk	Quote: "Unmarked plain tubes of the marketed formulation of each product were packed in plain sealed cartons, neither doctors nor patients being aware of the identity of the products until the end of the study." Comment: The outcome assessor, caregiver, and participant were probably blinded.
Incomplete outcome data (attrition bias)	Low risk	0/119 participants were omitted in the analysis: 0/65 in group 1, 0/54 in group 2.

Jaffe 1986 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Details of age, duration of condition, and total symptom severity score were recorded and were similar. There were no compliance data.
Randomised?	Low risk	Quote: "The trial was double-blind, patients being allocated at random to receive..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...who presented... were included in the study." Exclusion criteria was not specified.

Kennedy 1985

Methods	Time NR; Bristol, UK; general practice; only impetigo
Participants	• Average age 11 years (mupirocin), 17 years (neomycin) • M/F 2/1 • *S. aureus* 23/34, *S. pyogenes* 10/34 PNE
Interventions	A: mupirocin ointment 2%, 2 td, 10 to 11 days B: neomycin ointment 1%, 2 td, 10 to 11 days
Outcomes	**Outcomes of the trial** 1) Time of evaluation NR, cure/improved/failure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Allocation of treatment was on a randomized basis. In each consecutive group of four patients, two received Bactroban ointment and two received neomycin." Comment: They probably used blocked randomisation, but the process of selecting the blocks was not specified.
Allocation concealment (selection bias)	Unclear risk	It is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "The 15-g tubes differed only in their code numbers and in both cases the content was a white ointment." It is unclear how investigators were blinded. The caregiver and participant were probably blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	9/41 participants were omitted in the analysis: 8 were excluded due to a "stated diagnosis other than uncomplicated impetigo" (not stated which group), 1 missing from the mupirocin group due to "failure to attend to follow-up".

Kennedy 1985 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was baseline imbalance for age (mean 11 vs 17 years). There were no compliance data.
Randomised?	Low risk	Quote: "Allocation of treatment was on a randomized basis."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Patients were selected from those presenting with typical impetigo." Quote: "Patients were excluded if..."

Kiani 1991

Methods	Time NR; multicentre USA (Southern States); admitted + outpatients; range of skin infections (including impetigo 18/179)
Participants	• Age > 16, 211/154 (all participants) • *S. aureus* 152/179, *S. pyogenes* 29/179 (all participants) PE
Interventions	A: azithromycin 500 mg day 1, 250 mg, day 2 to 5, 5 days B: cephalexin 500 mg twice daily, 10 days
Outcomes	**Outcomes of the trial** 1) 11 days, cured/improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "In this double blind..." Quote: "Using a double-dummy technique, each patient received placebo capsules which were visually identical to the active drugs." Comment: The caregiver and participant were probably blinded. There was unclear blinding of the outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	High risk	187/366 participants were omitted in the analysis: 99/182 in the azithromycin group (58 due to "no baseline pathogen", 15 due to "no end of therapy assessment", 15 due to "the presence of a resistant pathogen" (only main reasons mentioned)), 88/184 in the cephalexin group (55 due to "no baseline pathogen", 6 due to "no end of therapy assessment", 6 due to "the presence of a resistant pathogen" (main reasons mentioned)). > 20% no end of therapy assessment (not specified for impetigo only).

Kiani 1991 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was a baseline comparison for sex, race, and primary diagnosis. There was no baseline imbalance. There were no compliance data.
Randomised?	Low risk	Quote: "Patients were randomly assigned in a double-blind fashion to one of the two treatment groups."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Patients were entered in the study based on..." Quote: "...were excluded by the protocol."

Koning 2003

Methods	February 1999 to November 2000; Rotterdam, Netherlands; general practice; only impetigo
Participants	• < 12, average age 5.0 years • M/F 98/62 • *S. aureus* 127/160, *S. pyogenes* 5/160, both 8/160, none 20/160 PNE
Interventions	A: fusidic acid cream 2%, 3 td + povidone iodine shampoo, 2 td B: placebo cream, 3 td + povidone iodine shampoo, 2 td
Outcomes	**Outcomes of the trial** 1) 7 days, cure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent statistician provided a computer-generated list of random set numbers in permuted blocks of six. The hospital pharmacist packed the study medication in identical blank tubes with a number according to the randomisation list."
Allocation concealment (selection bias)	Low risk	See above - probably done: central allocation.
Blinding (performance bias and detection bias) patient	Low risk	Quote: "Unblinding took place after the primary statistical analysis had been done." Quote: "....research nurse was unaware of treatment allocation." Quote: "...placebo cream did not differ." Quote: "Unblinding took place after the primary statistical analysis had been done." Comment: The outcome assessor, caregiver, and participant were probably all blinded.

Koning 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	4/160 participants were omitted in the analysis (after 1 week): 2/78 in the fusidic acid cream group (both did not want to follow up), 2/82 in the placebo cream group (both did not want to follow up).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance. There was more non-compliance in the placebo group.
Randomised?	Low risk	Quote: "Patients were randomised blockwise."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "General practitioners (GP's) in the Greater Rotterdam were asked to report patients aged 0-12 years with nonbullous impetigo presenting at their surgery." Quote: "Exclusion criteria were..."

Koning 2008

Methods	April to December 2005; India, Mexico, Netherlands, Peru; hospital outpatients and general practice patients; only impetigo
Participants	• 0 to 73 years of age, mean age around 11 years • M/F 107/103 • *S. aureus* 146/210, *S. pyogenes* 42/210
Interventions	A: topical retapamulin 1% 2 td for 5 days B: topical placebo 2 td for 5 days
Outcomes	**Outcomes of the trial** 1) Cured or improved after 7 days
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was centre based and performed using an automated telephone system."
Blinding (performance bias and detection bias) patient	Low risk	Quote: "The packaging and labelling of study medication was identical for the active medication and its placebo counterpart. All efforts were made to make the study medication and placebo identical with respect to appearance and smell." The outcome assessor, caregiver, and participant were all blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	50/213 participants missing in total: 18/140 in the retapamulin group (1 did not receive intervention, 17 withdrawals (5 lack of efficacy, 3 disease progression, 2 decided to withdraw, 1 adverse event, 5 lost to follow up)), 33/73 in the placebo group (2 did not receive intervention, 31 withdrawals (18 lack of effi-

Koning 2008 *(Continued)*

		cacy, 9 disease progression, 1 adverse event, 3 lost to follow up)). > 20% missing data.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Quote: "The mean total lesion area at baseline was larger in the retapamulin group compared with the placebo group." There was an imbalance for age. There were no compliance data.
Randomised?	Low risk	Quote: "We carried out a randomized..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Inclusion criteria were..." Quote: "...were excluded."

Koranyi 1976

Methods	1974; Columbus, Ohio, USA; outpatients; only impetigo
Participants	• 2 months to 15 years • M/F 14/16 • *S. aureus* 22/30, *S. pyogenes* 10/30 PNE
Interventions	A: bacitracin ointment 500 units/g, 4 td + oral placebo 6 days B: erythromycin 250 mg 4 td + placebo cream, 6 days
Outcomes	**Outcomes of the trial** 1) 6 days, cured/improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Drug assignment was based on a random distribution table, without the knowledge of the authors."
Allocation concealment (selection bias)	Low risk	See above.
Blinding (performance bias and detection bias) patient	Low risk	See above. Also double dummy design. The outcome assessor, caregiver, and participant were all blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/30 participants were omitted in the analysis: 0/15 in the bacitracin group, 0/15 in the erythromycin group.
Selective reporting (reporting bias)	Unclear risk	This was unclear.

Koranyi 1976 *(Continued)*

Other bias	Unclear risk	There was no baseline comparison for the most important prognostic factors. There were no compliance data.
Randomised?	Low risk	Quote: "Drug assignment was based on a random distribution table, without the knowledge of the authors."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...were enrolled in the study." Quote: "...were excluded."

Kuniyuki 2005

Methods	2002 to 2003; Japan; hospital outpatients; only impetigo
Participants	• 2 months to 13 years • M/F 27/22 • *S. aureus* 49/49 (inclusion criterion)
Interventions	A: topical tetracycline 3% 3 td + oral cefdinir 9 mg/kg/day for 7 days B: topical tetracycline 3% 3 td + oral minomycin 4 mg/kg/day for 7 days C: topical tetracycline 3% 3 td + oral fosfomycin 40 mg/kg/day for 7 days D: topical tetracycline 3% 3 td for 7 days
Outcomes	**Outcomes of the trial** 1) Cured, improved after 7 days
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was not reported.
Allocation concealment (selection bias)	Unclear risk	This was not reported.
Blinding (performance bias and detection bias) patient	High risk	Quote: "...open-label." The outcome assessor, caregiver, and participant were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only participants who were culture positive were analysed. The number of dropouts and withdrawals was not mentioned.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were no compliance data. There was a baseline comparison for age and sex - no imbalance.
Randomised?	Low risk	Quote: "...randomized".

Kuniyuki 2005 *(Continued)*

Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...were admitted to the study." Quote: "We excluded patients..."

McLinn 1988

Methods	February to May 1986 ; Scottsdale, Arizona, USA; outpatients; only impetigo
Participants	• > 6 months, average 5.5 years • *S.aureus* 43/60, *S.pyogenes* 17/60 PE
Interventions	A: mupirocin ointment 2%, 3 td, 7 to 9 days B: erythromycin 30 to 40/mg/kg/day in 3 to 4 doses, 7 to 9 days
Outcomes	**Outcomes of the trial** 1) 8 to 12 days, very much improved/ improved/no change
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized between the two treatment groups by a computer-generated set of random numbers in blocks of four."
Allocation concealment (selection bias)	Low risk	Quote: "...investigator was blinded to the treatment the patient was to receive at the time of patient entry."
Blinding (performance bias and detection bias) patient	High risk	Quote: "The investigator was blinded to the treatment the patient was to receive at the time of patient entry and was unblinded only in those cases where lesions persisted requiring additional culturing." Quote: "...open-label". This was not blinded for all participants. Also topical versus oral treatment. The outcome assessor and caregiver were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/60 participants were omitted in the analysis for clinical efficacy: 0/30 in the mupirocin group, 0/30 in the erythromycin group (2 participants in the erythromycin group discontinued therapy because of severe adverse experiences).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was a severe baseline imbalance, more fever in erythromycin group (12 versus 3), but they seem to have adjusted for this in the analysis. There were no compliance data.
Randomised?	Low risk	Quote: "Patients were randomized between the two treatment groups by a computer-generated set of random numbers in blocks of four."

McLinn 1988 *(Continued)*

Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...were enrolled in the study." Quote: "Patients with...were excluded."

Mertz 1989

Methods	Time NR; San Juan, Puerto Rico; outpatients; only impetigo
Participants	• 6 months to 32 years, average 5.4 years • M/F 27/26; *S.aureus* 44/53, GABHS 37/53 PE
Interventions	A: mupirocin ointment 2%, 3 td, 7 to 9 days C: erythromycin 30 to 50 mg/kg/day in 2 doses, 7 to 9 days
Outcomes	**Outcomes of the trial** 1) 7 to 9 days, cured/improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized between the two treatment groups according to a computer-generated schedule having a block size of four."
Allocation concealment (selection bias)	Low risk	See above, and Quote: "The randomization was predetermined by the sponsor and the schedule for distribution of medications was entrusted to a team member whose assignment was to dispense medication."
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "...were examined in a investigator-blinded study." Quote: "The randomization was predetermined by the sponsor and the schedule for distribution of medications was entrusted to a team member whose assignment was to dispense medication." Also, there was treatment with ointment versus capsules. The outcome assessor was blinded. The caregiver and the participant were not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	22/75 participants were omitted in the analysis: 9 were missing in the mupirocin group (unclear why), 13 were missing in the in the erythromycin group (unclear why).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was an imbalance for sex: 17/28 versus 10/25 boys (assessable participants) = 61% vs 40%. There was no compliance data.
Randomised?	Low risk	Quote: "Patients were randomized between the two treatment groups according to a computer-generated schedule having a block size of four."

Mertz 1989 *(Continued)*

Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Patients 3 months of age and older of either sex who had no more than seven lesions of impetigo, cellulitis, abscesses, or furunculosis were admitted to the study."

Montero 1996

Methods	Time NR; multicentre; Columbia Guatemala, Panama, South Africa; outpatients; range of skin infections (including impetigo 95/200)
Participants	• 6 months to 12 years • M/F 101/94 (all participants) • *S.aureus* 109/200, *S.pyogenes* 39/200 PNE
Interventions	A: azithromycin susp 10 mg/kg/day once daily, 3 days B: cefaclor susp 20 mg/kg/day in 3 doses, 10 days
Outcomes	**Outcomes of the trial** 1) 10 to 14 days, cured + improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly assigned in a 1:1 ratio to receive either..." It is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	High risk	Quote: "This open, comparative study..." Participants in both groups did not receive the same administrations of study drugs daily. Comment: The outcome assessor, caregiver, and participant were probably not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/100 participants were omitted in the analysis (all attritions): 2/100 in the azithromycin group (due to loss of follow up), 2/100 in the cefaclor group (due to loss of follow up).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance for gender, age, weight, height, and ethnic origin. There were no compliance data.
Randomised?	Low risk	Quote: "Patients were randomly assigned in a 1:1 ratio to receive either..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Two hundred children...entered this multicentre..." Quote: "Patients were excluded from the study if...shown in Table I."

Moraes Barbosa 1986

Methods	Time NR; Rio de Janeiro, Brasil; hospital outpatients; only impetigo
Participants	• Newborns, age 3 to 14 days, average 11 days • M/F 25/23 • *S.aureus* 100% (required for inclusion)
Interventions	4 arms: A: sodium fusidate ointment 2%, 3 td, 10 days B: chloramphenicol ointment, 3 td, 10 days C: neomycin/bacitracin ointment, 3 td, 10 days D: erythromycin oral 50 mg/kg/day, in 4 dd, 10 days
Outcomes	**Outcomes of the trial** 1) 7 days, cure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	High risk	Oral versus topical treatment. The outcome assessor, caregiver, and participant were probably not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 48 participants were analysed (see table 2).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were no differences for sex. No other characteristics were reported. There were no compliance data.
Randomised?	Low risk	Quote: "Estes foram divididos aleatoriamente em quatro grupos de 12." [They were randomly divided in 4 groups of 12.]
Were both inclusion and exclusion criteria specified?	High risk	Quote: "Quarenta e oito recem-nascidos entre tres e 14 dias de idade, portadores de impetigo estafilococico sem tratamento topica ou oral anterior, foram incluidos neste estudo." [40 and 8 neonates between 3 and 14 days old, who were carriers of impetigo stafylococcus without previous topical or oral treatment, had been enclosed in this study.] No exclusion criteria was specified.

Morley 1988

Methods	Time NR; Plymouth/Bristol, UK; general practice; range of skin infections (including impetigo 89/354)
Participants	• 1 to 92 years, average 33 years (all participants) • M/F 162/192 (all participants) • *S.aureus* 119/344, *S.pyogenes* 15/344, both 25/344 (all participants) PNE
Interventions	A: fusidic acid ointment 2%, 3 td, up to 7 days B: mupirocin ointment 2%, 3 td, up to 7 days
Outcomes	**Outcomes of the trial** 1) 6 to 8 days, excellent/good
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Low risk	Quote: "On entry, patients were allocated at random to receive one or other treatment, tubes of the ointment being provided in plain sealed numbered containers so that the investigator was unaware of the treatment given." Comment: This was probably done.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "On entry, patients were allocated at random to receive one or the other treatment, tubes of the ointment being provided in plain sealed numbered containers so that the investigator was unaware of the treatment given." Comment: The participants were probably blinded because the tubes were plain sealed. The outcome assessor was blinded. It is unclear whether the caregiver was blinded (it is unclear if the outcome assessor was also the caregiver).
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/354 participants were omitted in the analysis: 0/191 in the sodium fusidate group, 0/163 in the mupirocin group. Therapy was withdrawn in only 2 cases - 1 in each treatment group.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was baseline comparison for sex, age, and severity. There were no compliance data.
Randomised?	Low risk	Quote: "On entry, patients were allocated at random to receive one or other treatment."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "The study involved 354 patients with acute superficial skin sepsis amenable to therapy with a topical antibiotic." Quote: "Patients who...were excluded." Quote: "...were also exclusion factors."

Nolting 1988

Methods	Time NR; Münster, Germany; outpatients; range of skin infections (including impetigo 66/80)
Participants	• 1 to 65 years, average 24 years • M/F 35/31 • *S.aureus* 41/66, GABHS 8/66, both 17/66 PE
Interventions	A: sulconazole nitrate cream 1%, 2 td, 14 days B: miconazole nitrate cream 2%, 2 td, 14 days
Outcomes	**Outcomes of the trial** 1) 7 days/14 days, cure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "When patients enrolled in the trial, they were allocated, according to a computer-generated randomization code, to receive either..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "...double-blind, parallel comparative study". It is unclear if, and how, the outcome assessor, caregiver, and participant were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/80 participants were omitted in the analysis: 0/40 in the sulconazole group, 0/40 in the miconazole group.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	The proportion of micro-organisms isolated at admission differs between groups (19 vs 6 for *streptococcus,* 53 vs 71 for *S. aureus*). There were no compliance data.
Randomised?	Low risk	Quote: "...according to a computer-generated randomization code..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Patients...were admitted to the trial." Quote: "...were excluded from the trial."

Oranje 2007

Methods	2005; Canada, Costa Rica, France, Germany, India, The Netherlands, Peru, Poland, South Africa; outpatients; only impetigo
Participants	• 9 months to 84 years

Oranje 2007 *(Continued)*

	• M/F 278/239 • *S. aureus* 341/517, *S. pyogenes* 137/517
Interventions	A: topical retapamulin 1% 2 td for 5 days B: topical sodium fusidate 2% 3 td for 7 days
Outcomes	**Outcomes of the trial** 1) Cure or improvement after 7 (retapamulin) or 9 days (sodium fusidate)
Notes	Randomisation was 2:1.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was not reported.
Allocation concealment (selection bias)	Low risk	Quote: "...predetermined, center-based 2:1 schedule using the telephone-based interactive, central Registration and Medication Ordering System."
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "...observer-blinded..." Quote: "...helped protect investigator blinding." Quote: "To maintain observer blinding..." Participants in both groups did not receive the same administrations of study drugs daily. Participants were not blinded, the outcome assessor was blinded, and the blinding of the caregiver is unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	41/519 participants were missing data in both groups: 26/346 in the retapamulin group (26 prematurely discontinued, of which 8 had disease progression, 8 were lost to follow up, 1 had adverse events, 1 through lack of efficacy, 1 through protocol violation, 1 through potential conflicts of interest, 3 through 'other'), 15/172 in the sodium fusidate group (15 prematurely discontinued, of which 6 had disease progression, 1 was lost to follow up, 1 through subject decision [participant decision?], 3 had adverse events, 1 through lack of efficacy, 3 through 'other'), 1/519 were not included in the analysis.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance. Compliance was comparable.
Randomised?	Low risk	Quote: "This was a randomised..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Subjects were included if..." Quote: "Subjects were excluded if..."

Pruksachat 1993

Methods	December 1988 to November 1990; Chiang Mai, Thailand; outpatients; only impetigo
Participants	• 1 months to 8 years, median 3.5 years

Pruksachat 1993 *(Continued)*

	• M/F 64/46 (all participants) • *S. aureus* 77/110 PE
Interventions	A: penicillin V potassium 50 mg/kg/day in 4 doses, 7 days B: cloxacillin sodium 50 mg/kg/day in 4 doses, 7 days
Outcomes	**Outcomes of the trial** 1) 7 days, cure
Notes	Bullous and non-bullous impetigo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	It is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	High risk	This was not mentioned in the article: If the outcome assessor, caregiver, or participant was not blinded, he or she is likely to cause bias. All 3 were probably not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	20/110 participants were omitted in the analysis: 45 were treated in the penicillin group and 45 were in the cloxacillin group (9 were unavailable for follow-up and 11 were negative to culture - not specified per group).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were no baseline characteristics per group. There were no compliance data.
Randomised?	Low risk	Quote: "Participants were randomly assigned to receive either..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Children... were invited to participate in the study." Quote: "Inclusion criteria included..."

Rice 1992

Methods	April to November 1989; Baltimore, USA; outpatients and general practice; only impetigo
Participants	• 3 months to 16 years • MF 53/30 • Culture only in case of therapy failure PNE
Interventions	A: erythromycin ethynyl succinate 40 mg/kg/day in 4 doses, 10 days B: mupirocin ointment 2%, 3 td, 10 days

Rice 1992 *(Continued)*

Outcomes	**Outcomes of the trial** 1) 9 to 11 days, cure/improved/failure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	It is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	High risk	Quote: "In any clinical trial that is not blinded..." Also, oral versus topical treatment. The outcome assessor, caregiver, and participant were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/93 participants were omitted in the analysis. The following were specified: 4/46 in the erythromycin group (4 did not return for follow-up), 6/47 in the mupirocin group (4 did not return for follow-up, 2 were excluded from completing the protocol, 1 had cellulites develop within a few hours after entry into the study, 1 whose primary provider added an oral antibiotic to the treatment regimen on day 3 of therapy even though the participant's condition was improving).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Low risk	The baseline characteristics were comparable. Compliance was good and comparable (table 6).
Randomised?	Low risk	Quote: "Children were randomly assigned to the two study groups."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "All children... were invited to participate." Quote: "Exclusion criteria included..."

Rist 2002

Methods	Time NR; USA; outpatients; secondary impetigo (all eczema)
Participants	• 9 to 87 years • M/F 87/72 • *S. aureus* 74/159, *S. pyogenes* 0/159
Interventions	A: topical mupirocin 2% 3 td + oral placebo for 10 days B: oral cephalexin 250 mg 4 td + topical placebo for 10 days
Outcomes	**Outcomes of the trial** 1) Cured or improved after 12 to 13 days

Rist 2002 *(Continued)*

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Low risk	Quote: "...double-blind, double-dummy, parallel-group trial..." The outcome assessor, caregiver, and participant were all blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	33/159 (> 20%) participants did not complete the study (not specified per group). All 159 were in the ITT analysis. Participants whose outcome was indeterminable were considered failures. This may have introduced bias.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Quote: "Compliance was similar for both groups." Quote: "The mean SIRS scores were 20.5 for the mupirocin group and 19,1 for the cephalexin group (P = 0.09)." There was an imbalance for sex.
Randomised?	Low risk	Quote: "In this randomized..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Patients were eligible for entry into the trial if..." Quote: "Patients were excluded from the study if..."

Rodriguez-Solares 1993

Methods	Time NR; multicentre; Costa Rica, Guatemala, Panama, Venezuela; outpatients; range of skin infections (including impetigo 39/118)
Participants	• 2 to 12 years, mean 5 years • M/F NR • *S. aureus* 69/118, *S. pyogenes* 9/118 (all participants) PNE
Interventions	3 arms: A: azithromycin 10 mg/kg/day (max. 500), once daily, 3 days B: dicloxacillin12.5 to 25 mg/kg/day in 4 doses, 7 days (see notes) C: flucloxacillin 500 to 2000 mg/day in 4 doses (see notes)
Outcomes	**Outcomes of the trial** 1) 7 to 10 days, cure/improved/failure
Notes	Randomisation was between azithromycin and, either, dicloxacillin or flucloxacillin; the treatment groups dicloxacillin and flucloxacillin are combined in the results

Rodriguez-Solares 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was provided.
Blinding (performance bias and detection bias) patient	High risk	Quote: "An open, randomized..." The outcome assessor, caregiver, and participant were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant was missing (in which group was not specified).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline comparison (or compliance data) for the subgroup of impetigo participants.
Randomised?	Low risk	Quote: "An open, randomized..." Quote: "60 were randomized to receive..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Children...were eligible to enter this study." Quote: "Concurrent treatment with...was not permitted." Quote: "The principal exclusion criteria were..." Quote: "Persons were also excluded if..."

Rojas 1985

Methods	Time NR; Dominican Republic; hospital outpatients; only impetigo
Participants	• Age and M/F ratio NR • Bacterial results NR PE
Interventions	A: mupirocin ointment 2%, 3 td, 10 to 12 days B: placebo/vehicle, 3 td, 10 to 12 days
Outcomes	**Outcomes of the trial** 1) 7 to 12 days, cure/improved
Notes	-

Risk of bias

Rojas 1985 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "The medication was numerically labelled; the protocol ensured double-blind comparisons." Bactroban ointment versus vehicle ointment. It is not clear whether the caregiver and outcome assessor are the same person. There was unclear blinding of the outcome assessor. The participant and the caregiver were probably blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Fifty patients completed the study." The number of participants that entered into the study was not specified.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline data. There were no compliance data.
Randomised?	Low risk	Bactroban ointment versus vehicle ointment - so, probably randomised but not clearly described.
Were both inclusion and exclusion criteria specified?	High risk	Quote: "Patients with...entered in the study sequentially." No exclusion criteria was specified.

Ruby 1973

Methods	Summer 1972; Dallas, USA; outpatients; only impetigo
Participants	• Children, age NR • M/F 43/59 • Only GABHS 33/102, both *S. aureus* and GABHS 57/102 PNE
Interventions	5 arms: A: phenoxymethyl penicillin 40 to 60,000 units/kg/day in 3 doses + HS B: phenoxymethyl penicillin 40 to 60,000 units/kg/day in 3 doses C: HS + placebo D: placebo, 3 td E: bacitracin ointment, 2 td
Outcomes	**Outcomes of the trial** 1) 5 days, cure
Notes	-
Risk of bias	

Ruby 1973 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to one of five treatment groups by a random numbers list." Quote: "When more than one child from an household was entered in the study, all those children received the same treatment." Comment: This was probably done.
Allocation concealment (selection bias)	High risk	Quote: "Patients were assigned to one of five treatment groups by a random numbers list." Quote: "When more than one child from an household was entered in the study, all those children received the same treatment." Investigators knew that children in the same household got the same treatment.
Blinding (performance bias and detection bias) patient	High risk	Quote: "Phenoxymethyl penicillin suspension and placebo were coded as 'impecillin' and 'tigocillin'". Also, ointment versus suspension. The bacitracin was not placebo-controlled. Comment: The outcome assessor, caregiver, and participant were probably not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	24/102 participants were omitted in the analysis: 0/20 in group A (penicillin + hexachlorophene), 2/20 in group B (penicillin) (2 not streptococcal positive), 12/23 in group C (placebo) (6 not streptococcal positive, 6 failed to return for first follow-up), 4/17 in group D (placebo+hexachlorophene) (2 not streptococcal positive, 2 failed to return for first follow-up;), 6/22 in group E (bacitracin) (2 not streptococcal positive, 4 failed to return for first follow-up).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance. Compliance was good for penicillin (based on urine test) but not reported for other therapy.
Randomised?	Low risk	Quote: "Patients were assigned to one of five treatment groups by a random numbers list."
Were both inclusion and exclusion criteria specified?	High risk	Quote: "Children with... were excluded." Quote: "All patients were seen".

Sutton 1992

Methods	Time NR; UK; general practice (n = 20); only impetigo (only facial)
Participants	• 1 months to 77 years, average 22 years • M/F 84/93 • *S. aureus* 68/177 PNE
Interventions	A: fusidic acid cream 3 td, 6 to 8 days B: mupirocin ointment 3 td, 6 to 8 days

Sutton 1992 *(Continued)*

Outcomes	**Outcomes of the trial** 1) 8 days, cure + improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was provided.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "Investigators were not aware of the treatment given until the study was completed." Quote: "Treatment was allocated randomly in a double-blind manner, medication [was] dispensed in numbered, sealed containers." There was unclear blinding of the caregivers because it is unclear whether this is the same person as the outcome assessor. The participants were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	24/201 were omitted in the analysis: 93 were left in the fusidic acid group, 84 were left in the mupirocin group (not further specified). 177/201 were in the analysis. Of the 24 participants who were not analysed for efficacy, 20 returned for follow-up after more than 8 days, 2 defaulted, and 2 violated the study protocol.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance. There were no compliance data.
Randomised?	Low risk	Quote: "Treatment was allocated randomly in a double-blind manner."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "A total of 201 patients requiring topical antibiotic treatment for facial impetigo were enrolled". Quote: "Exclusion criteria were..."

Tack 1997

Methods	1992 July to 1993 August; multicentre; US; outpatients; range of skin infections (including impetigo 225/394)
Participants	• 0 to 13 years (median 5.4) • M/F 217/197 • *S. aureus* 284/394 (all participants) PE
Interventions	A: cefdinir 7 mg/kg/day , 2 td, 10 days B: cephalexin 10 mg/kg/day, 4 td, 10 days

Tack 1997 *(Continued)*

Outcomes	**Outcomes of the trial** 1) 7 to 14 day, cure
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was provided.
Allocation concealment (selection bias)	Unclear risk	It is unclear whether participants and investigators enrolling participants could foresee assignment.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "...a multicenter, randomized, controlled, investigator-blind..." Also, participants in both groups did not receive the same administrations of study drugs daily. The outcome assessor was blinded. The caregiver and participant were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "...number of patients excluded for each reason comparable among groups." The proportion of participants not evaluable for reasons of non-compliance was unclear. Quote: "An intention-to-treat analysis was also performed. This analysis counted as failures all patients who had negative admission cultures or for whom follow-up information was not available."
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance (sex, age, race, infection type). There were no compliance data.
Randomised?	Low risk	Quote: "...a multicenter, randomized, controlled, investigator-blind..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Pediatric patients...were eligible for study entry." Quote: "Patients were prohibited from entering the study if..."

Tack 1998

Methods	January to December 1992; multicentre; USA; outpatients, range of skin infections (including impetigo 62/952)
Participants	• 13 to 88 years • M/F 564/388 (all participants) • *S. aureus* 308/382 (all participants) PE
Interventions	A: cefdinir caps 300 mg, 2 td, 10 days B: cephalexin caps 500 mg, 4 td, 10 days
Outcomes	**Outcomes of the trial**

Tack 1998 *(Continued)*

	1) 7 to 16 days, cure/improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was provided.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "This was a double-mask, comparative, multicenter study." Quote: "Matched placebo capsules were dispensed appropriately to maintain study masking." It is not clear who was blinded (and how). It is unclear whether the outcome assessor and caregiver were blinded. The participants were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	952 randomised participants. Quote: "Of these, 178 cefdinir patients and 204 cephalexin patients were considered microbiologically assessable and were included in the efficacy analyses." > 20% not included in efficacy analysis because they were not assessed or the study drug was not taken as prescribed (table III). There was no intention-to-treat analysis.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Groups were similar at baseline (table II), though not specified for impetigo participants. There were no compliance data.
Randomised?	Low risk	Quote: "Patients were randomized 1:1 to receive..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Eligible patients were..." Quote: "Exclusion criteria included..."

Tamayo 1991

Methods	Time NR; Mexico; outpatients; only impetigo
Participants	• 6 months to 12 years, average 4 years 8 months • M/F 14/16 • *S. aureus* 18/30, *S. pyogenes* 4/30, both 1/30 PE: not clear
Interventions	A: rifamycin spray, 2 td, 7 days B: mupirocin ointment 2%, 2 td, 7 days
Outcomes	**Outcomes of the trial**

Tamayo 1991 *(Continued)*

	1) 1 week, cure/improved
Notes	Both primary (n = 17) and secondary (n = 13) impetigo participants were studied.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	High risk	Quote: "...open trial". Also, spray versus ointment. The caregiver, outcome assessor, and participant were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/30 participants were omitted in the analysis: 0/15 in the rifamycin group, 0/15 in the mupirocin group.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance. There were no compliance data.
Randomised?	Low risk	Quote: "...fueron asignados al azar." [...were assigned at random.]
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "En este estudio únicamente se incluyeron pacientes con lesiones localizades, con área no mayor de 10 cm^2 Los criterios de exclusión fueron niños con lesiones con un tiempo de evolución mayor de un mes." [In this study, patients were only included if the lesions were smaller than 10 cm^2. Exclusion criteria were children with lesions present longer than 1 month].

Tassler 1993

Methods	Time NR; multicentre; Europe and South America; hospital-admitted and outpatients; range of skin infections (including impetigo 42/172)
Participants	• Age 18 to 99 years • M/F 159/125 (all part) • *S. aureus* 58% (all participants) PE
Interventions	A: fleroxacin 400 mg, 1 td, 7 to 21 days B: amoxicillin/clavulanic acid tablets 500/125 mg, 3 td, 7 to 21 days
Outcomes	**Outcomes of the trial** 1) 7 days, cure
Notes	-

Risk of bias

Tassler 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available
Blinding (performance bias and detection bias) patient	High risk	Quote: "...open-label". Participants in both groups did not receive the same administrations of study drugs daily. Also, investigators enrolling participants could possibly foresee assignment. The outcome assessor, caregiver, and participant were not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not only impetigo - it was not specified how many impetigo participants were randomised and included. 27 were analysed in the fleroxacin group, 15 were analysed in the amoxicillin/clavulanic group. Further data was not specified for impetigo participants. Not all participants were assessable for the efficacy analysis, but it was not stated how many.
Selective reporting (reporting bias)	Unclear risk	This was not unclear.
Other bias	Unclear risk	There was no baseline imbalance. There were no compliance data.
Randomised?	Low risk	Quote: "This study was designed as a prospective, randomized, open label..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Inpatients or outpatients of either sex were eligible for inclusion in the study if..." Quote: "Exclusion criteria were..."

Vainer 1986

Methods	March 1982 to January 1984; Denmark; general practice; only impetigo
Participants	• Age 1 to 77, average 11 years • M/F 71/57 • No bacterial culture done PNE
Interventions	3 arms: A: fusidic acid cream 2% B: tetracycline/polymyxin B ointment C: neomycin/bacitracin ointment
Outcomes	**Outcomes of the trial** 1) 1 week, cure/improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Vainer 1986 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "Undersøgelsen var således blindet for lægen, men ikke for patienten." [The study was blinded for the doctor, but not for the patient.] The outcome assessor and caregiver were blinded. Participants were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/134 participants were not included in the analysis: unknown group assignment, reasons were given.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was no baseline imbalance for severity. The used medication is in table 2. There were no compliance data.
Randomised?	Low risk	Quote: "...randomiseringsnummer." [...randomisation number.]
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "For at indgå i study skulle patienterne have klinisk verificeret impetigo"; "Udelukket var patienter med impetigeniserede eksemer, patienter med..." [Patients were eligible if they had clinical verified impetigo; Excluded were patients with impetiginised eczema and patients with...]

Wachs 1976

Methods	1974; multicentre; USA; outpatients; only impetigo (secondary)
Participants	• Age/sex NR • *S. aureus* 62/79 PNE
Interventions	3 arms: A: betamethasone valerate cream, 3 td B: gentamycin cream, 3 td C: betamethasone + gentamycin cream, 3 td
Outcomes	**Outcomes of the trial** 1) 3 weeks, excellent result
Notes	Secondary impetigo (impetiginised atopic dermatitis)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.

Wachs 1976 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information was available
Blinding (performance bias and detection bias) patient	Low risk	Quote: "...precautions being observed to preserve the blinding of both patients and therapists." Also, participants in both groups received the same administrations of study drugs daily. The outcome assessor, caregiver, and participant were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/83 participants were omitted in the analysis (not further specified).
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was a baseline comparison for severity and no imbalance. There were no compliance data.
Randomised?	Low risk	Quote: "Patients under the care of an individual investigator were randomly assigned."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "All patients enrolled were clinically judged to have moderate to severe impetiginized..." Quote: "In order to be accepted for the study..." Quote: " ...were excluded."

Wainscott 1985

Methods	Time NR; London, UK; outpatients and general practice; range of skin infections (including impetigo 16/39)
Participants	• Age NR • M/F 25/14 (all participants) • *S. aureus* 31/48 (all participants) PE: not clear
Interventions	A: mupirocin ointment 2%, 2 td, 7 to 14 days B: chlortetracycline cream 3%, 2 td, 7 to 14 days
Outcomes	**Outcomes of the trial** 1) 7 days, cure/improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.

Wainscott 1985 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "Thirty-nine patients were entered in a randomized, observer-blind trail." Quote: "...but the medications were packaged identically and not opened in the presence of the physician." The outcome assessor and caregiver were blinded. Participants were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/39 participants were omitted in the analysis: 2/22 in the mupirocin group, 1/17 in the chlortetracycline group. These 3 were excluded from the analysis of results as they received systemic antibiotics for other infections while in the study.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There was a baseline imbalance for age (all infants were in the Bactroban group). This was not specified for impetigo. There were no compliance data.
Randomised?	Low risk	Quote: "Thirty-nine patients were entered in a randomized, observer-blind trail."
Were both inclusion and exclusion criteria specified?	High risk	Quote: "Patients with lesions suitable for treatment with a topical antibiotic were entered in the study." No exclusion criteria was specified.

Welsh 1987

Methods	Time NR; Monterrey, Mexico; outpatients; range of skin infections (including impetigo 15/60)
Participants	• Age NR • M/F 32/28 • *S. aureus* 47/50 PNE
Interventions	A: mupirocin ointment 2%, 3 td, 5 to 10 days B: ampicillin 50 mg, 4 td, 5 to 10 days
Outcomes	**Outcomes of the trial** 1) 10 days, cure/improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.

Welsh 1987 *(Continued)*

Blinding (performance bias and detection bias) patient	High risk	Quote: "...in an open trial." Thereby, the participants in both groups did not receive the same administrations of study drugs daily. The outcome assessor, caregiver, and participant were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/60 participants were omitted in the analysis: 5/32 in the mupirocin group were lost to follow up, 5/28 in the ampicillin group were lost to follow up. These 10 participants were not analysed.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Quote: "Patient characteristics were similar in both treatment group in terms of sex, age, and weight." Table I shows no baseline imbalance for severity. There were no compliance data.
Randomised?	Low risk	Quote: "A randomized clinical trial..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "...outpatients with primary and secondary skin infections." Quote: "Patients were excluded from entry into the trial on the basis of..."

White 1989

Methods	1985 to 1987; UK; general practice; range of skin infections (including impetigo 155/390)
Participants	• Age 11 months to 84 years • M/F NR • *S. aureus* 43% (all participants) PNE
Interventions	A: mupirocin ointment 2%, 2 td, 7 days B: fusidic acid ointment 2%, 3 td, 7 days
Outcomes	**Outcomes of the trial** 1) 7 days, cure/improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.
Allocation concealment (selection bias)	Low risk	Quote: "...and patients were randomised to receive treatment with either..." Quote: "For this purpose, a code was designed in blocks of six..." Quote: "The tubes were supplied in a sealed box labelled with the patient's number. Thereby the observer did not know which antibiotic a patient was receiving." Comment: This was probably done.

White 1989 *(Continued)*

Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "Four plain tubes containing the preparations were supplied for each patient. These were labelled with instructions for use but the name of the antibiotic was omitted. Mupirocin was to be applied twice daily and sodium fusidate thrice daily." Quote: "The tubes were supplied in a sealed box labelled with the patient's number. Thereby the observer did not know which antibiotic a patient was receiving." The outcome assessor was blinded. The caregiver and participant were probably not blinded because they did not receive the same administrations of study drugs daily.
Incomplete outcome data (attrition bias) All outcomes	High risk	23/413 participants were omitted in the analysis: 12/275 in the mupirocin group (8 failed to attend for assessment, 1 withdrew due to revised diagnosis, 3 were prescribed antibiotics for reasons other than lack of efficacy), 11/138 in the sodium fusidate group (3 failed to attend for assessment, 1 withdrew due to revised diagnosis, 2 were prescribed antibiotics for reasons other than lack of efficacy, 4 due to non-compliance, 1 due to inadequate data). < 20% dropouts, but reasons were not balanced between the groups.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	Quote: "There was a similar distribution of type and severity of infection between the two treatment groups". There were no compliance data.
Randomised?	Low risk	Quote: "...observer-blind randomised multi-centre clinical trial."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Any patient with primary or secondary skin infection, other than...was eligible for entry." Quote: "Patients were excluded if..."

Wilkinson 1988

Methods	Time NR; Quebec, Canada; outpatients; range of skin infections (including impetigo 10/50)
Participants	• Age/sex NR • *S. aureus* 18/50 (all participants) PE: not clear
Interventions	A: mupirocin 2%, 3 td, 7 days B: polymyxin B-neomycin (Neosporin), 3 td, 7 days
Outcomes	**Outcomes of the trial** 1) 7 days, cure/improved
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information was available.

Wilkinson 1988 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information was available.
Blinding (performance bias and detection bias) patient	Unclear risk	Quote: "...double-blind fashion." It was unclear how, and if, the outcome assessor, caregiver, and participant were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 0/10 missing impetigo participants: 0/4 missing in the mupirocin group, 0/6 missing in the neosporin group.
Selective reporting (reporting bias)	Unclear risk	This was unclear.
Other bias	Unclear risk	There were no baseline characteristics. There were no compliance data.
Randomised?	Low risk	Quote: "...were randomly divided into..."
Were both inclusion and exclusion criteria specified?	Low risk	Quote: "Fifty patients who appeared at the dermatologic clinic with primary and secondary skin infections of...were randomly divided..." Quote: "...were excluded from the trial."

all participants = data from all participants in the study, not just the impetigo participants
Abbreviations:
approx = approximately
GABHS = Group A beta Hemolytic Streptococcus
HS = hexachlorophene scrubs
M/F = male/female
NR = not reported
PE = participants excluded from study when culture negative
PNE = participants not excluded
SE = side-effects
susp = suspension
td = times daily
m = months
dd = daily doses
ds = days

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alavena 1987	Randomisation was inadequate.
Anonymous 1998	Results were not separately described for impetigo participants: no randomisation.
Arata 1983	Randomisation was inadequate (serial allocation).
Arata 1994	The results were not separately described for impetigo participants.
Arosemena 1977	The results were not separately described for impetigo participants: only 6/343 participants had impetigo.
Azimi 1999	The results were not separately described for impetigo participants.

Study	Reason for exclusion
Baldwin 1981	The same drug was compared.
Ballantyne 1982	The results were not separately described for impetigo participants: no randomisation.
Bastin 1982	The results were not separately described for impetigo participants.
Bernard 1997	The results were not separately described for impetigo participants (requested, but no reply).
Bin Jaafar 1987	No participants had impetigo ("pyoderma").
Burnett 1963	There was no randomisation.
Cassels-Brown 1981	The design was unacceptable (no RCT).
Colin 1988	The results were not separately described for impetigo participants.
Cordero 1976	There was only 1 impetigo participant.
De Waard 1967	There was no randomisation: 2 arms with the same active drug (though different mode of administration).
Dillon 1970	There was no randomisation.
Dillon 1979a	The results were not separately described for impetigo participants.
Drehobl 1997	The results were not separately described for impetigo participants (requested, but no reply).
el Mofty 1990	The results were not separately described for impetigo participants.
Esterly 1970	There was no randomisation.
Faingezicht 1992	The results were not separately described for impetigo participants.
Fedorovskaia 1989	Randomisation was inadequate.
Fleisher 1983	The results were not separately described for impetigo participants.
Forbes 1952	The same drug was compared.
Free 2006	No participants had impetigo (communication: Nicole E. Scangarella).
Gentry 1985	The results were not separately described for impetigo participants.
Gibbs 1987	All impetigo participants received the same treatment.
Golcman 1997	The results were not separately described for impetigo participants (requested, but no reply).
Goldfarb 1987	The results were not separately described for impetigo participants.
Gooch 1991	The results were not separately described for impetigo participants.
Hanfling 1992	The results were not separately described for impetigo participants.
Harding 1970	There was 1 drug (flucloxacillin) in 2 doses: the results for impetigo participants were not separately described.

Study	Reason for exclusion
Heskel 1992	The results were not separately described for impetigo participants.
Jacobs 1992	The results were not separately described for impetigo participants.
Jennings 1999	There was only 1 impetigo participant.
Jennings 2003	The results were not separately described for impetigo participants (requested, but no reply).
Keeny 1979	The results were not separately described for impetigo participants.
Kotrajaras 1973	The results were not separately described for impetigo participants.
Kumakiri 1988	There was only 1 impetigo participant.
Kumar 1988	No participants had impetigo: 2 forms of the same drug.
Lassus 1990	The results were not separately described for impetigo participants.
Lentino 1984	There was only 1 impetigo participant.
Levenstein 1982	The results were not separately described for impetigo participants.
Lewis-Jones 1985	The results were not separately described for impetigo participants.
Linder 1978	The results were not separately described for impetigo participants.
Linder 1993	The results were not separately described for impetigo participants.
Lipets 1987	No comparison was made.
Liu 1986	No participants had impetigo (impetigo herpetiformis).
MacKenna 1945	Randomisation (serial allocation) was inadequate.
Macotela-Ruiz 1988	The results were not separately described for impetigo participants (requested, but no reply).
Mallory 1991	The results were not separately described for impetigo participants.
Manaktala 2009	The results were not separately described for impetigo participants.
McCarty 1992	The results were not separately described for impetigo participants.
McMillan 1969	The results were not separately described for impetigo participants.
Milidiú d Silva 1985	The results were not separately described for impetigo participants.
Nakayama 1983	The results were not separately described for impetigo participants, and it was not an RCT.
Neldner 1991	The results were not separately described for impetigo participants.
Nichols 1997	The results were not separately described for impetigo participants.
Nicolle 1990	The results were not separately described for impetigo participants.
Nolting 1992	No participants had impetigo (pyoderma).

Study	Reason for exclusion
Orecchio 1986	The results were not separately described for impetigo participants.
Pakrooh 1978	No participants had impetigo.
Palazzini 1993	The results were not separately described for impetigo participants.
Parish 1984	The results were not separately described for impetigo participants.
Parish 1991	The results were not separately described for impetigo participants.
Parish 1992	The results were not separately described for impetigo participants.
Parish 1997	The results were not separately described for impetigo participants.
Parish 2000	The results were not separately described for impetigo participants (requested, but no data available).
Parish 2006	No participants had impetigo (communication: Nicole E. Scangarella).
Park 1993	There was no randomisation (personal communication: Seungsoo Sheen).
Pien 1983	The results were not separately described for impetigo participants.
Powers 1991	There were no separate results for clinical cure.
Powers 1993	There were only 2 impetigo participants.
Pusponegoro 1990	There was only 1 impetigo participant,
Risser 1985	The results were not separately described for impetigo participants.
Saenz 1985	The results were not separately described for impetigo participants.
Salzberg 1972	There was only 1 impetigo participant.
Schupbach 1992	The results were not separately described for impetigo participants.
Schwartz 1996	There was only 1 impetigo participant.
Smith 1985	The results were not separately described for impetigo participants.
Smith 1993	There was only 1 impetigo participant.
Sobye 1966	The results were not separately described for impetigo participants.
Stevens 1993	There were 5 participants with "pyoderma".
Tack 1991	The results were not separately described for impetigo participants, and the same drug was compared.
Török 2004	The same drug was compared.
Urbach 1966	No randomisation was described.
Van der Auwera 1985	No participants had impetigo.

Study	Reason for exclusion
Villiger 1986	The results were not separately described for impetigo participants.
Wachs 1992	The results were not separately described for impetigo participants.
Wible 2003	The results were not separately described for impetigo participants (requested, but no reply).
Wolbling 1987	2 doses of 1 drug were compared.
Wong 1989	The results were not separately described for impetigo participants.
Yura 1988	The results were not separately described for impetigo participants.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Chen 2011

Methods	This is an RCT.
Participants	• Age 6 months to 18 years with uncomplicated skin and soft tissue infections
Interventions	**Intervention** A: clindamycin **Control intervention** B: cephalexin
Outcomes	**Primary outcomes of the trial** 1) Improvement **Secondary outcomes of the trial** 1) Complete resolution
Notes	This is a result of the CSG searches that were run in August 2011. It is not known how many participants were impetigo patients.

Chosidow 2005

Methods	This is an RCT.
Participants	• Various skin infections (including impetigo)
Interventions	**Intervention** A: cloxacillin **Control intervention** B: pristinamycin
Outcomes	**Outcomes of the trial**

Chosidow 2005 *(Continued)*

	1) Cure
Notes	This will be included when data on impetigo participants is provided.

Davies 1945

Methods	Please see the 'notes' cell below.
Participants	Please see the 'notes' cell below.
Interventions	Please see the 'notes' cell below.
Outcomes	Please see the 'notes' cell below.
Notes	This is a result of the CSG searches that were run in August 2011. We were unable to obtain a copy of this trial.

Ghosh 1995

Methods	This is possibly an RCT.
Participants	• 70 participants of different ages suffering from pyoderma, including infective dermatitis of which 30 participants had impetigo
Interventions	**Intervention** A: neem, haldi, sajina, and garlic oil (Nutriderm oil) **Control intervention** B: gentian violet
Outcomes	**Primary outcomes of the trial** 1) Cure **Secondary outcomes of the trial** 1) Side-effects
Notes	-

Gubelin 1993

Methods	Please see the 'notes' cell below.
Participants	Please see the 'notes' cell below.
Interventions	Please see the 'notes' cell below.
Outcomes	Please see the 'notes' cell below.

Gubelin 1993 *(Continued)*

Notes	This paper was published in Spanish, and we were unable to obtain a copy.

Kar 1988

Methods	This is possibly an RCT.
Participants	• 200 children suffering from various types of pyoderma, 94 of which had impetigo
Interventions	**Intervention** A: injection benzathine penicillin **Control intervention** B: oral sulphamoxole
Outcomes	**Outcomes of the trial** 1) Cure after 1 and 2 weeks
Notes	There did not appear to be separate results for impetigo.

Kar 1996

Methods	This is possibly an RCT.
Participants	• 200 children aged 10 months to 12 years suffering from pyoderma
Interventions	**Intervention** A: 125 mg amoxicilin plus 30 mg clavulanate per 5 ml of suspension, equivalent to 20 mg amoxicillin/kg/day in 3 divided doses **Control interventions** B: amoxicillin 20 mg/kg/day in 3 divided doses C: erythromycin 30 mg/kg/day in 4 divided doses D: co-trimoxazole (8 mg trimethoprim + 40 mg sulfamethoxazole/kg/day) in 2 divided dosis
Outcomes	**Primary outcomes of the trial** 1) Presence of *S. aureus* **Secondary outcomes of the trial** 1) Cure 2) Adverse events
Notes	It was not clear if pyoderma equated to impetigo.

Luby 2002

Methods	This is an RCT.
Participants	• 162 households in Pakistan
Interventions	**Intervention** A: 1.2% triclocarban-containing soap **Control intervention** B: an identically appearing placebo
Outcomes	**Outcomes of the trial** 1) Impetigo incidence
Notes	This is a result of the CSG searches that were run in August 2011.

Menendez 2007

Methods	This is possibly an RCT.
Participants	• 136 children (1 day to 14 years) with impetigo
Interventions	**Intervention** A: sunflower oil **Control intervention** B: mupirocin
Outcomes	**Primary outcomes of the trial** 1) Clinical cure after possibly 6 days
Notes	This paper was written in Spanish.

Motohiro 1992

Methods	This is an RCT.
Participants	Please see the 'notes' cell below.
Interventions	Please see the 'notes' cell below.
Outcomes	Please see the 'notes' cell below.
Notes	This is a result of the CSG searches that were run in August 2011. We were unable to obtain a copy of this trial.

Pierard-Franchimont 2008

Methods	This is an RCT.
Participants	Please see the 'notes' cell below.
Interventions	Please see the 'notes' cell below.
Outcomes	Please see the 'notes' cell below.
Notes	This is a result of the CSG searches that were run in August 2011. We were unable to obtain a copy of this trial.

Sharquie 2000

Methods	This is possibly an RCT.
Participants	• 104 participants with impetigo
Interventions	**Intervention** A: tea lotion B: tea ointment C: soframycin D: oral cephalexin
Outcomes	**Primary outcomes of the trial** 1) Cure after 7 to 10 days
Notes	-

Suchmacher 2010

Methods	This is an RCT.
Participants	Please see the 'notes' cell below.
Interventions	Please see the 'notes' cell below.
Outcomes	Please see the 'notes' cell below.
Notes	This is a result of the CSG searches that were run in August 2011. We were unable to obtain a copy of this trial.

Tong 2010

Methods	This is a pilot study.

Tong 2010 *(Continued)*

Participants	• 13 participants with skin sores
Interventions	**Intervention** A: oral cotrimoxazole B: intramuscular benzathine penicillin
Outcomes	**Primary outcomes of the trial** 1) Resolution of skin sores
Notes	Australian Trial Register: Is cotrimoxazole safe and efficacious for treatment of skin sores in Aboriginal children: a pilot study Published in the Journal of Pediatrics and Child Health 2010;46:131-133

Wang 1988

Methods	This is possibly an RCT.
Participants	Please see the 'notes' cell below.
Interventions	Please see the 'notes' cell below.
Outcomes	Please see the 'notes' cell below.
Notes	We were unable to obtain a copy of this trial.

Wang 1995

Methods	This is possibly an RCT.
Participants	Please see the 'notes' cell below.
Interventions	Please see the 'notes' cell below.
Outcomes	Please see the 'notes' cell below.
Notes	We were unable to obtain a copy of this trial.

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12609000858291

Trial name or title	An open label randomised controlled trial to determine if 5 days of once-daily oral trimethoprim-sulfamethoxazole or three days of twice-daily oral trimethoprim-sulfamethoxazole will lead to non-inferior cure rates of impetigo compared to a single dose of intramuscular benzathine penicillin G (the current gold standard treatment) in children living in remote Aboriginal communities between the age of 12 weeks to less than 13 years
Methods	See title.

ACTRN12609000858291 *(Continued)*

Participants	**Inclusion criteria of the trial** 1. Age 12 weeks to less than 13 years at the time written consent is obtained 2. Diagnosis of purulent or crusted impetigo by criteria outlined in the Booklet "Recognising and Treating Skin Conditions" (East Arnhem Healthy Skin Program (EAHSP), Menzies School of Health Research 2006) 3. A resident in 1 of the participating (Aboriginal) communities at the time of enrolment and intending to stay in that community for the duration of the study (7 days post-randomisation)
Interventions	Group 1: single dose intramuscular benzathine penicillin G - weight band-based dosing up to 900 mg (> 3 and < 6 kg = 225 mg; > 6 and < 10 kg = 337.5 mg; > 10 and < 15 kg = 450 mg; > 15 and < 20 kg = 675 mg; > 20 kg = 900 mg) Group 2: trimethoprim-sulfamethoxazole oral suspension 8 + 40 mg/kg (max 320 + 1600 mg) daily for 5 days Group 3: trimethoprim-sulfamethoxazole oral suspension 4 + 20 mg/kg (max 160 + 800 mg) twice daily for 3 days
Outcomes	**Primary outcomes of the trial** 1) The proportion of children successfully treated on day 7 after the commencement of treatment within each of the respective groups. Successfully treated is defined as a child with impetigo which has been clinically classified as sore either healed or improved by a person blinded to the allocated randomisation **Secondary outcomes of the trial** 1) The proportion of children within each of the respective groups who are defined as being successfully treated on day 2 2) Prevalence of *Staphylococcus aureus* (methicillin susceptible and methicillin resistant) and Group A Streptococci per child at day 0, day 2, and day 7 within each treatment group as determined from impetigo swabs collected at the respective time points 3) Effect of each treatment on the bacterial resolution of sores at days 2 and 7 as determined by impetigo swabs collected at the respective time points 4) Prevalence of nasal carriage of *Staphylococcus aureus* at baseline and day 7 (including a comparison of the prevalence of methicillin-resistant *S. aureus* at baseline and day 7) 5) Evidence of allergy or other reaction to the medication within 7 days of first administration as determined by clinical observation and questioning of caregivers
Starting date	1st December 2009
Contact information	Ross Andrews (ross.andrews@menzies.edu.au) Menzies School of Health Research PO Box 41096 Casuarina, 0811, NT, Australia
Notes	Australian New Zealand Clinical Trial Registry: ACTRN12609000858291

CTRI/2008/091/000060

Trial name or title	An Open Labelled, Double Arm, Randomized, Multicentric, Prospective And Comparative, Phase-III Trial To Evaluate The Safety And Efficacy Of Fixed Dose Combination Of Ceftriaxone And Vancomycin Injection Vs. Vancomycin Injection In Subjects With Various Bacterial Infections

CTRI/2008/091/000060 *(Continued)*

Methods	See above.
Participants	**Inclusion criteria of the trial** • All subjects aged between 18 and 70 years • Diagnosed subjects of infectious disease (on clinical evaluation). • Subjects willing to give informed consent • Subject suffering from any of the following infections - lower respiratory tract infections, skin and skin structure infections, endocarditic, bacterial meningitis and bone infection
Interventions	See above.
Outcomes	**Primary outcomes of the trial** 1) Compare the efficacy of a 3.0 g FDC of ceftriaxone and vancomycin injection vs 1.0 g vancomycin injection in subjects with mild to severe bacterial infections **Secondary outcomes of the trial** 1) Evaluate the safety of the test and comparative product
Starting date	8th April 2008
Contact information	kundan.k@nexuscro.com
Notes	It is unclear whether impetigo participants will be included.

NCT00202891

Trial name or title	Sisomicin Cream Vs Nadifloxacin Cream in Primary Pyodermas
Methods	This was to be a randomised, active-control trial. End point classification - safety/efficacy study Intervention model - parallel assignment Masking - open-label Primary purpose - treatment
Participants	**Inclusion criteria of the trial** • Participants of either sex, suffering from primary pyodermas requiring topical antibiotic therapy without occlusive dressing, > = 6 years of age • Written informed consent
Interventions	See title.
Outcomes	None were stated.
Starting date	May 2007
Contact information	Ragunandan Torsekar, MD, FCPS (Principal Investigator) Rajiv Gandhi Medical College

NCT00202891 *(Continued)*

Notes	The current status of the trial is withdrawn (NCT00202891).

NCT00626795

Trial name or title	Efficacy, Safety, and Tolerability of TD1414 2% Cream in Impetigo and Secondarily Infected Traumatic Lesions (SITL)
Methods	Quote: "This is an international, multicentre, prospective 3-arm parallel-group, phase II proof of concept study comparing the efficacy and safety of 2 dosage regimens (BID 7 days and TID 7 days) of TD1414 2% cream and 1 dosage regimen (BID 7 days) of Bactroban® (mupirocin) 2% cream in adults and children down to 2 years of age with impetigo or SITL. Furthermore, an evaluation of the pharmacokinetics of TD1414 2% cream TID for 7 days will be performed. A total of 664 patients will be enrolled in a stepwise manner according to age groups starting with the oldest age group."
Participants	See above.
Interventions	See above.
Outcomes	**Primary outcomes of the trial** 1) Clinical cure at end of treatment according to investigator's assessment **Secondary outcomes of the trial** 1) Clinical cure at follow-up according to investigator's assessment 2) Clinical cure at end of treatment and follow-up according to investigator's assessment 3) Bacteriological cure at end of treatment and follow-up
Starting date	February 2008
Contact information	Almena L Free, MD (Principal Investigator) Anniston Medical Clinic Anniston, Alabama, United States 36207
Notes	www.clinicaltrials.gov

NCT00852540

Trial name or title	A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Safety and Efficacy of Topical Retapamulin Ointment, 1%, Versus Oral Linezolid in the Treatment of Secondarily-Infected Traumatic Lesions and Impetigo Due to Methicillin-Resistant Staphylococcus Aureus
Methods	See above.
Participants	See above.
Interventions	See above.
Outcomes	**Primary outcomes of the trial**

NCT00852540 *(Continued)*

	1) Number of participants achieving clinical response at follow-up who had methicillin-resistant *Staphylococcus aureus* (MRSA) as a baseline pathogen **Secondary outcomes of the trial** 1) Number of participants achieving microbiological response at follow-up who had MRSA as a baseline pathogen 2) Number of participants with clinical response at follow-up 3) Number of participants who achieved microbiological response at follow-up who had a baseline pathogen 4) Number of participants with the indicated clinical outcome at the end of therapy who had MRSA as a baseline pathogen 5) Number of participants with the indicated microbiological outcome at the end of therapy who had MRSA as a baseline pathogen 6) Number of participants with the indicated clinical outcome at the end of therapy 7) Number of baseline pathogens with the indicated microbiological outcome at the end of therapy 8) Number of participants with therapeutic response at follow-up 9) Mean scores on the skin infection rating scale at visits 1, 2, 3, 4, and 5 10) Mean wound size at visits 1, 2, 3, 4, and 5
Starting date	April 2009
Contact information	Study Director GSK Clinical Trials GlaxoSmithKline
Notes	-

NCT00986856

Trial name or title	A Phase IV Study Comparing Clinical and Bacteriological Efficacy of Fucidin® Cream With Fucidin® Cream Vehicle in the Treatment of Impetigo in Paediatric Patients
Methods	This is a randomised, placebo-controlled trial. End point classification - safety/efficacy Study Intervention model: parallel assignment Masking - double-blind (subject, investigator) Primary purpose - treatment
Participants	**Inclusion criteria of the trial** • Participants with a clinical diagnosis of impetigo • Participants aged 2 to 11 years • Participants of either sex • Participants whose parent(s) has/have provided written consent

NCT00986856 *(Continued)*

	• Participants with a severity score of 1 for at least 1 of the following signs: pustules/infected bullae, erythema, or infiltration/induration
Interventions	A: Fucidin® cream versus Fucidin® cream vehicle
Outcomes	**Primary outcomes of the trial** 1) The proportion of participants with clinical success (marked improvement or completely cleared) and bacteriological success (eradication) at end of treatment (EOT) **Secondary outcomes of the trial** 1) The proportion of participants with clinical and bacteriological success at visit 2 and 3, and at EOT 2) The actual change in Total Severity Score from baseline to end of treatment 3) The distribution of individual sign scores at end of treatment
Starting date	May 2004
Contact information	Inga Odenholt (Principal Investigator) Malmö University Hospital
Notes	Infomation was obtained from clinicaltrials.gov. Information was requested in August 2010.

NCT01171326

Trial name or title	A Randomized, Parallel-group, Double Blind, Clinical Trial, to Asses the Safety and Efficacy of Topically Applied FXFM244 Antibiotic Foam in the Treatment of Impetigo
Methods	This is a randomised, parallel-group, double (Investigator, participant)-blind, comparative dose range-finding clinical trial.
Participants	**Inclusion criteria of the trial** • Participants with clinical diagnosis of pure impetigo, impetigo contagiosa, or uncomplicated blistering impetigo • Participants 2 years of age or older and in general good health • Participants with no less than 2 lesions and no more than 7 lesions (area 0.5 x 0.5 cm) • No known medical conditions that, in the Investigator's opinion, could interfere with study participation • Participant/participant's guardian (in the case of children) willing and able to comply with all requirements of the protocol • Participant/participant's guardian willing and able to give written informed consent prior to participation in the study
Interventions	The study will involve 2 treatment groups. A: Eligible participants will be randomised to receive either FXFM244 - 1% or FXFM244 - 4% in a blinded fashion. Participants will be treated twice daily for 7 days. Following the screening period and baseline visit, study subjects will return at days 3, 7 and 14. At each visit, participants will be evaluated via lesion count, global assessment tolerability, and safety.
Outcomes	**Primary outcomes of the trial** 1) Decrease in lesion count 7 days **Secondary outcomes of the trial**

NCT01171326 *(Continued)*	1) The severity of the overall impetigo condition will be measured at baseline and at all follow-up visits. The severity will be assessed and graded based on the scales for Investigator's Global Assessment and bacteriological testing (days 3, 7, and 14)
Starting date	August 2010
Contact information	Foamix Ltd. Lev Yasmin Clinic Natanya, Israel
Notes	This study is probably not eligible for inclusion as 2 dosages of the same drug are used.

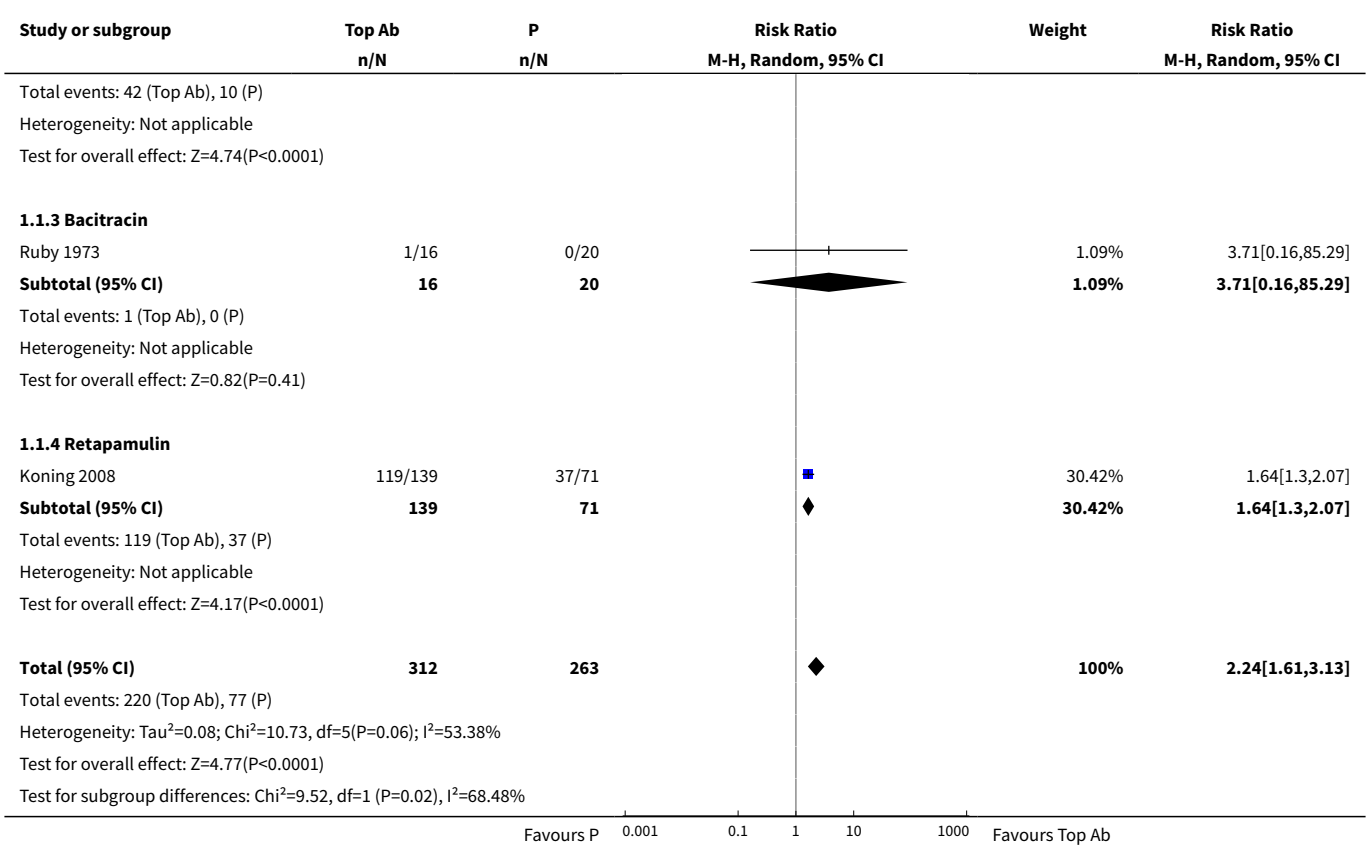
DATA AND ANALYSES

Comparison 1. Non-bullous impetigo: topical (Top) antibiotic (Ab) vs placebo (P)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	6	575	Risk Ratio (M-H, Random, 95% CI)	2.24 [1.61, 3.13]
1.1 Mupirocin	3	173	Risk Ratio (M-H, Random, 95% CI)	2.18 [1.58, 3.00]
1.2 Fusidic acid	1	156	Risk Ratio (M-H, Random, 95% CI)	4.42 [2.39, 8.17]
1.3 Bacitracin	1	36	Risk Ratio (M-H, Random, 95% CI)	3.71 [0.16, 85.29]
1.4 Retapamulin	1	210	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.30, 2.07]

Analysis 1.1. Comparison 1 Non-bullous impetigo: topical (Top) antibiotic (Ab) vs placebo (P), Outcome 1 Cure/improvement.

Study or subgroup	Top Ab n/N	P n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Mupirocin					
Eells 1986	14/17	8/19		17.38%	1.96[1.1,3.46]
Gould 1984	10/14	7/21		14.07%	2.14[1.08,4.27]
Rojas 1985	34/50	15/52		20.95%	2.36[1.48,3.76]
Subtotal (95% CI)	**81**	**92**		**52.39%**	**2.18[1.58,3]**
Total events: 58 (Top Ab), 30 (P)					
Heterogeneity: Tau^2=0; Chi^2=0.25, df=2(P=0.88); I^2=0%					
Test for overall effect: Z=4.76(P<0.0001)					
1.1.2 Fusidic acid					
Koning 2003	42/76	10/80		16.09%	4.42[2.39,8.17]
Subtotal (95% CI)	**76**	**80**		**16.09%**	**4.42[2.39,8.17]**
		Favours P	0.001 0.1 1 10 1000	Favours Top Ab	

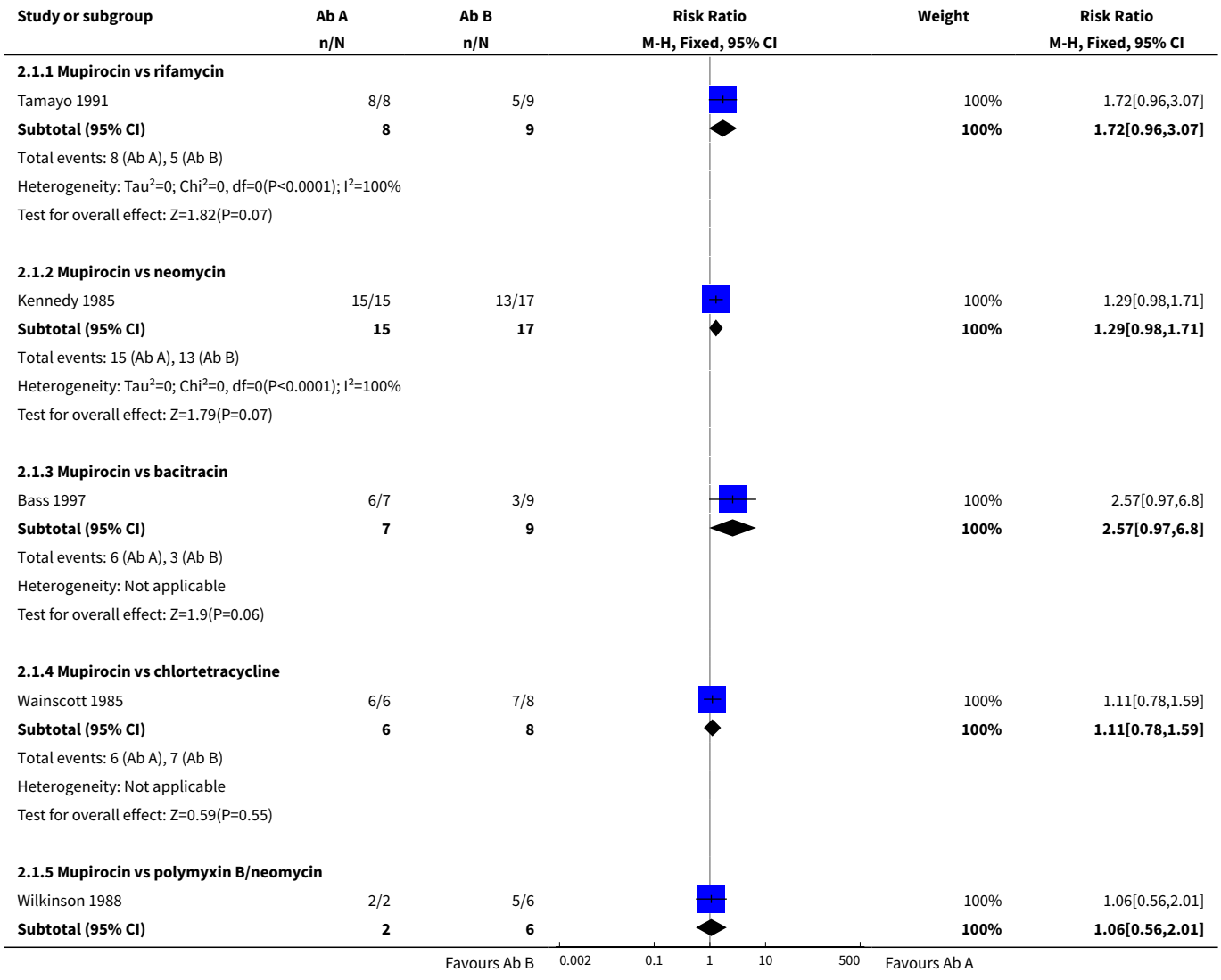


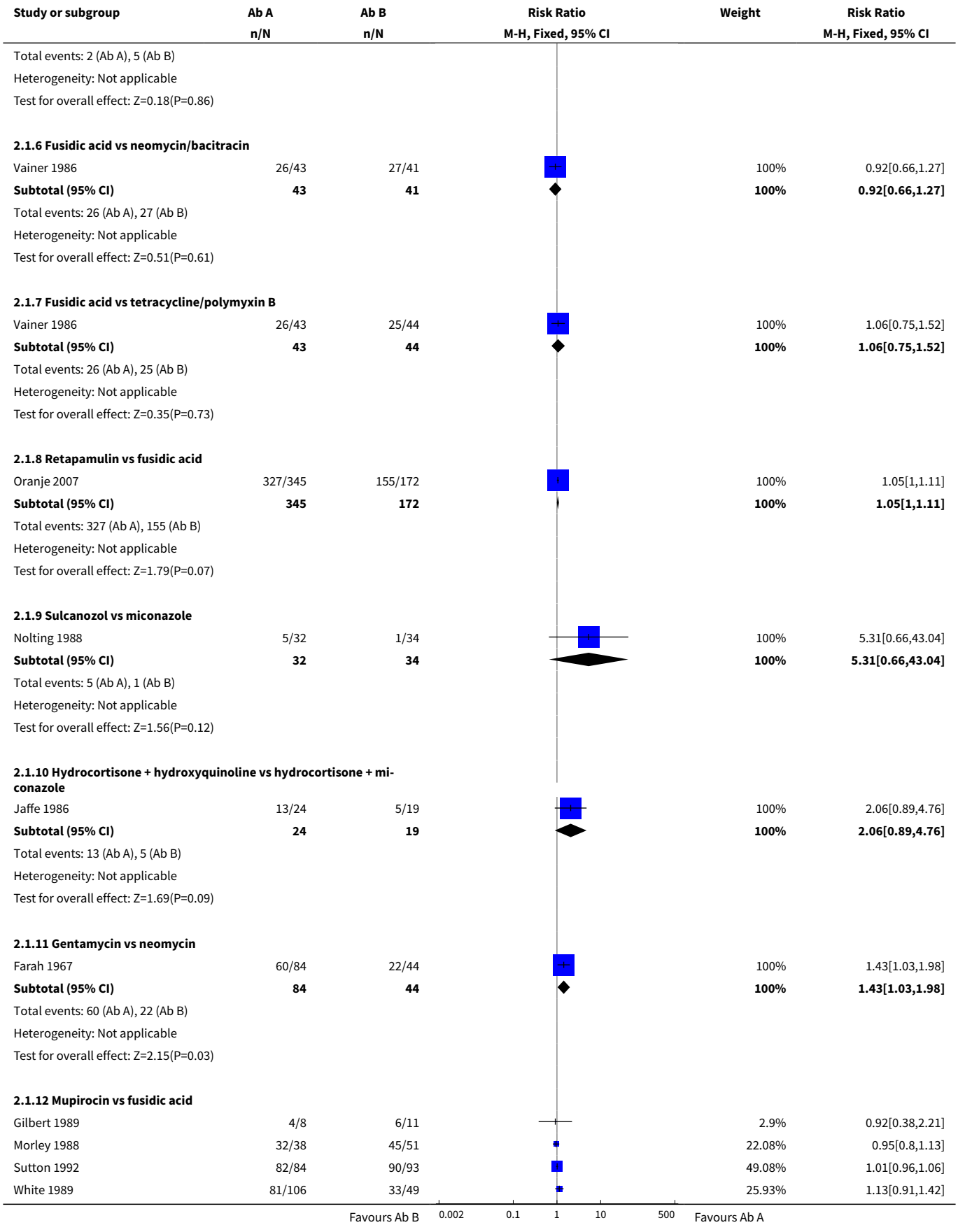
Comparison 2. Non-bullous impetigo: topical (Top) antibiotic (Ab) vs another topical (Top) antibiotic (Ab)

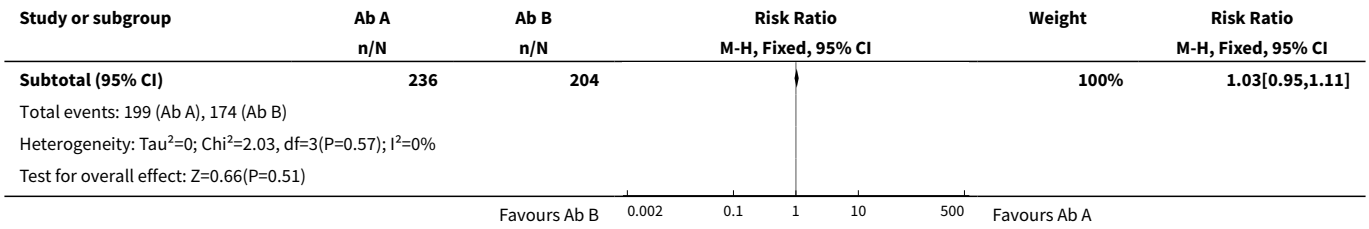
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	14		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Mupirocin vs rifamycin	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.96, 3.07]
1.2 Mupirocin vs neomycin	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.98, 1.71]
1.3 Mupirocin vs bacitracin	1	16	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [0.97, 6.80]
1.4 Mupirocin vs chlortetracycline	1	14	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.78, 1.59]
1.5 Mupirocin vs polymyxin B/neomycin	1	8	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.56, 2.01]
1.6 Fusidic acid vs neomycin/bacitracin	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.66, 1.27]
1.7 Fusidic acid vs tetracycline/polymyxin B	1	87	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.75, 1.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8 Retapamulin vs fusidic acid	1	517	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [1.00, 1.11]
1.9 Sulcanozol vs miconazole	1	66	Risk Ratio (M-H, Fixed, 95% CI)	5.31 [0.66, 43.04]
1.10 Hydrocortisone + hydroxyquinoline vs hydrocortisone + miconazole	1	43	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.89, 4.76]
1.11 Gentamycin vs neomycin	1	128	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.03, 1.98]
1.12 Mupirocin vs fusidic acid	4	440	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.11]

Analysis 2.1. Comparison 2 Non-bullous impetigo: topical (Top) antibiotic (Ab) vs another topical (Top) antibiotic (Ab), Outcome 1 Cure/improvement.



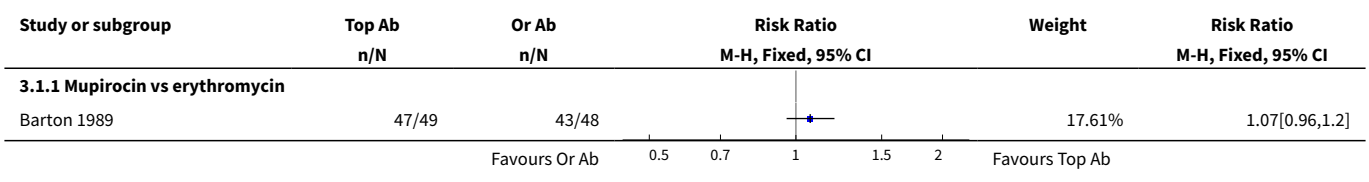


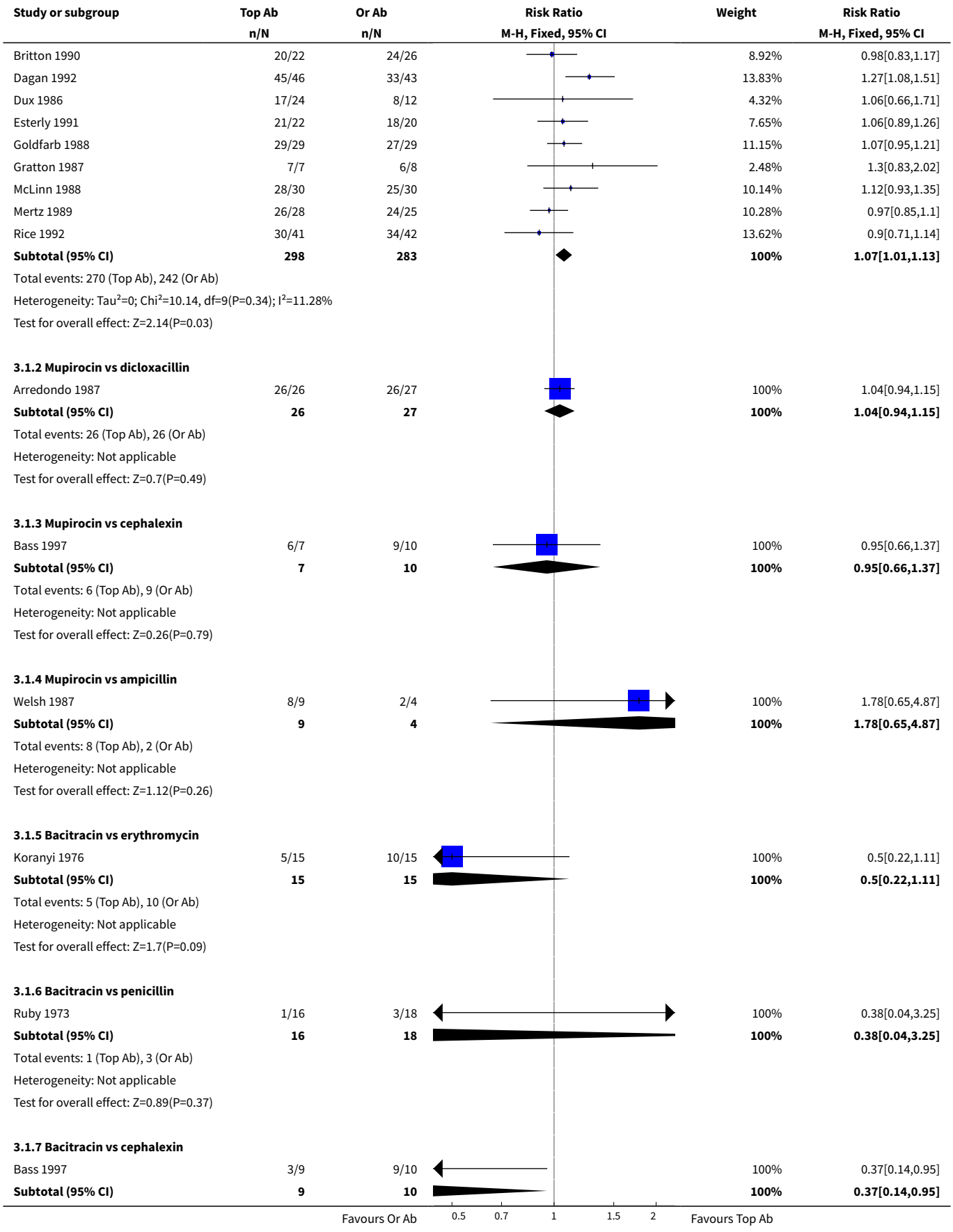


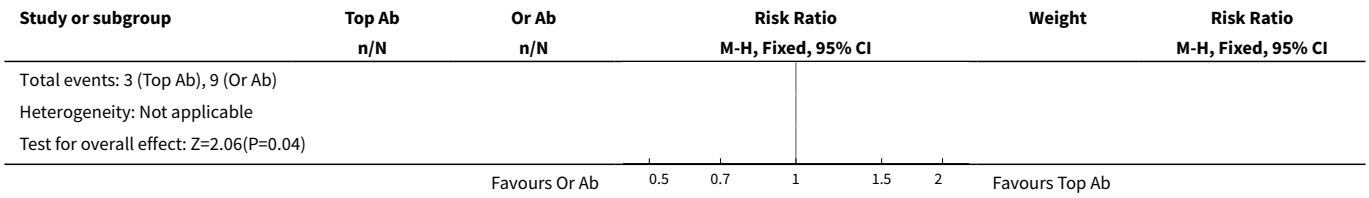
Comparison 3. Non-bullous impetigo: topical (Top) antibiotic (Ab) vs oral (Or) antibiotic (Ab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	15		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Mupirocin vs erythromycin	10	581	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [1.01, 1.13]
1.2 Mupirocin vs dicloxacillin	1	53	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.94, 1.15]
1.3 Mupirocin vs cephalexin	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.66, 1.37]
1.4 Mupirocin vs ampicillin	1	13	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.65, 4.87]
1.5 Bacitracin vs erythromycin	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.22, 1.11]
1.6 Bacitracin vs penicillin	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.04, 3.25]
1.7 Bacitracin vs cephalexin	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.14, 0.95]
2 Cure/improvement	2	137	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.86, 1.46]
2.1 Mupirocin vs erythromycin: observer blinded studies	2	137	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.86, 1.46]

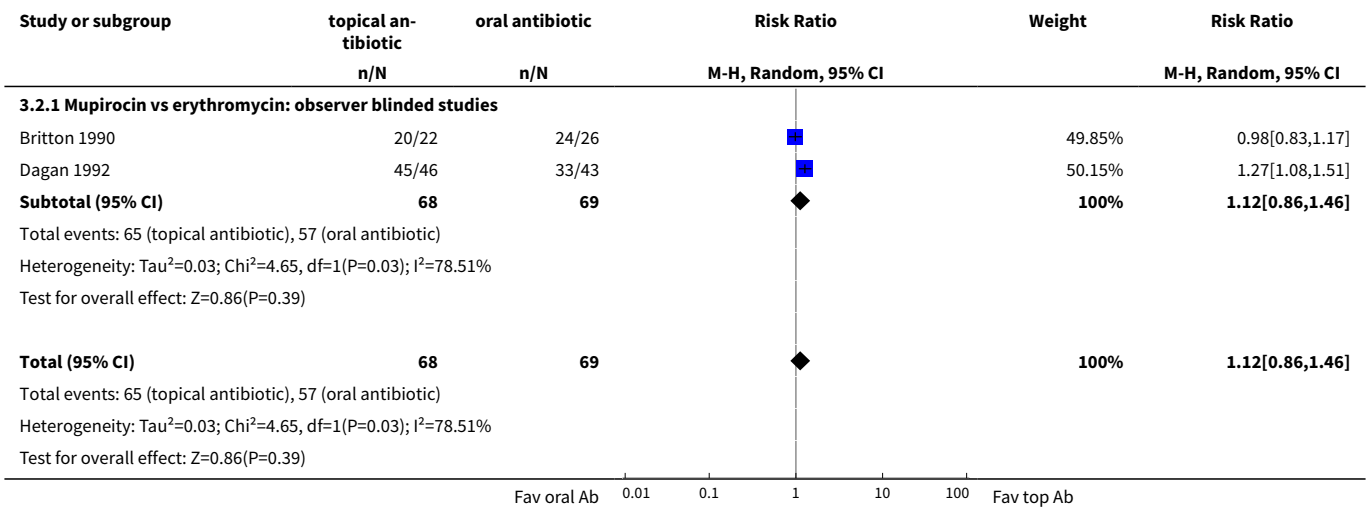
Analysis 3.1. Comparison 3 Non-bullous impetigo: topical (Top) antibiotic (Ab) vs oral (Or) antibiotic (Ab), Outcome 1 Cure/improvement.







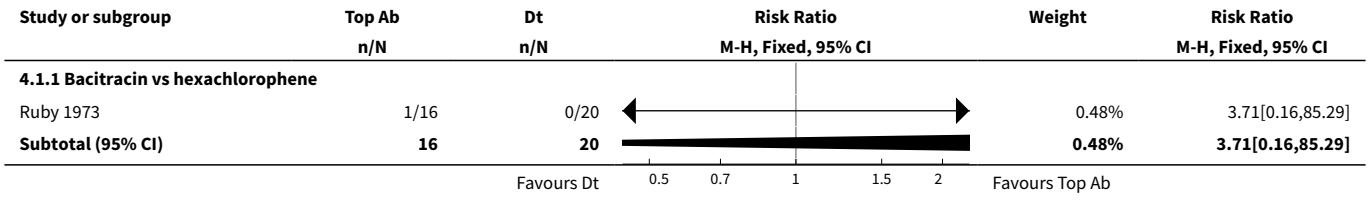
Analysis 3.2. Comparison 3 Non-bullous impetigo: topical (Top) antibiotic (Ab) vs oral (Or) antibiotic (Ab), Outcome 2 Cure/improvement.

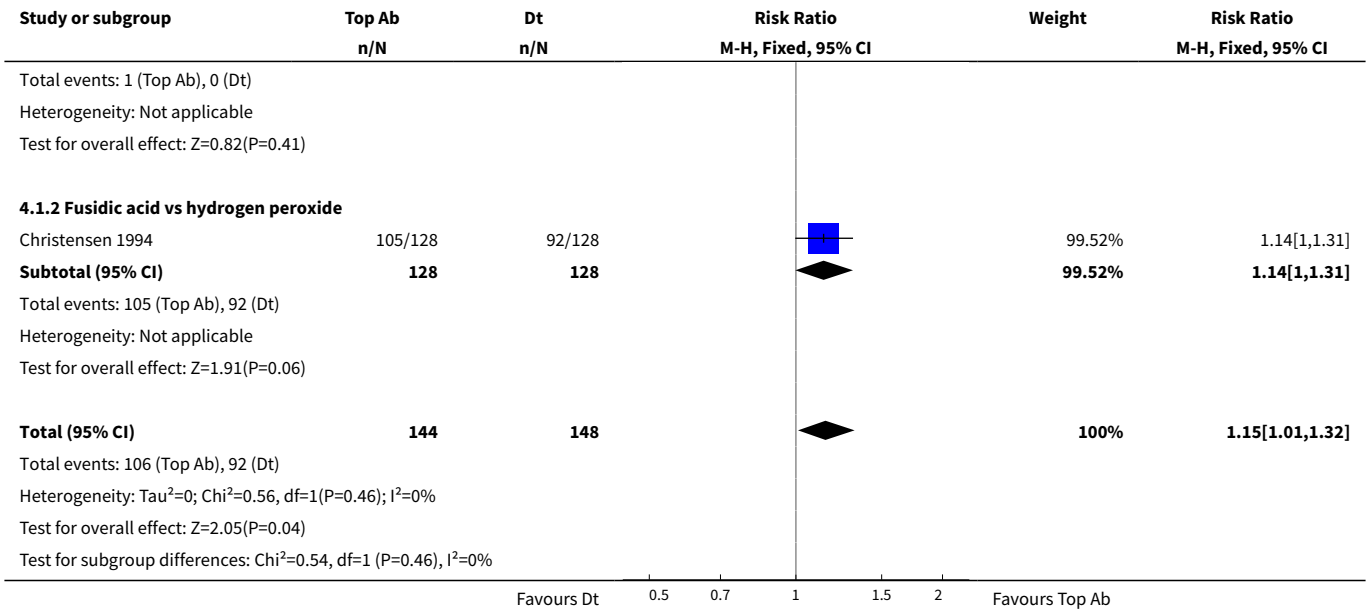


Comparison 4. Non-bullous impetigo: topical (Top) antibiotic (Ab) vs disinfecting treatments (Dt)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	2	292	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.01, 1.32]
1.1 Bacitracin vs hexachlorophene	1	36	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [0.16, 85.29]
1.2 Fusidic acid vs hydrogen peroxide	1	256	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.00, 1.31]

Analysis 4.1. Comparison 4 Non-bullous impetigo: topical (Top) antibiotic (Ab) vs disinfecting treatments (Dt), Outcome 1 Cure/improvement.

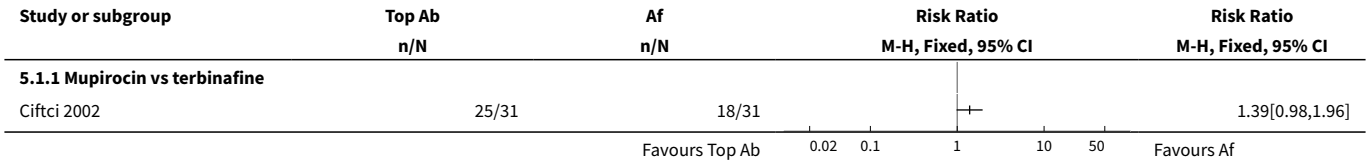




Comparison 5. Non-bullous impetigo: topical (Top) antibiotic (Ab) vs antifungal (Af)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Mupirocin vs terbinafine	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Non-bullous impetigo: topical (Top) antibiotic (Ab) vs antifungal (Af), Outcome 1 Cure.

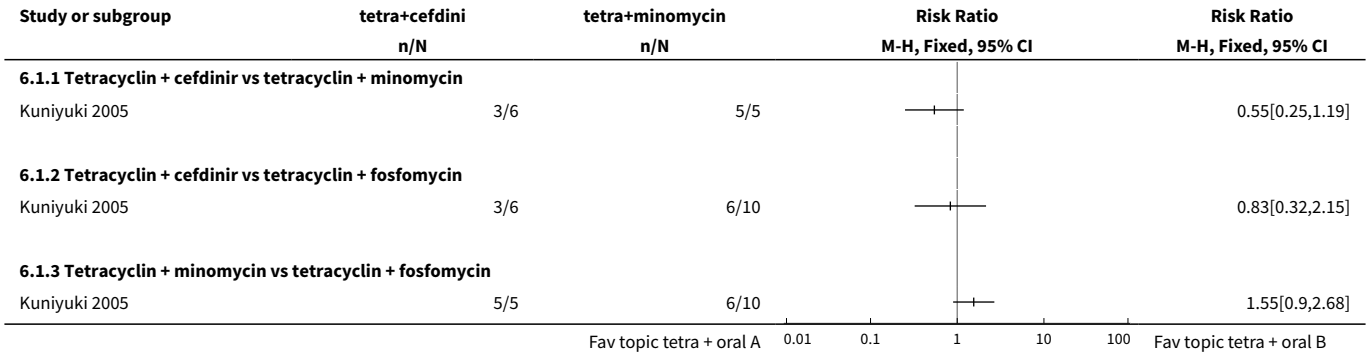


Comparison 6. Non-bullous impetigo: topical (Top) antibiotic (Ab) + oral (Or) antibiotic (Ab) vs topical (Top) antibiotic (Ab) + oral (Or) antibiotic (Ab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Tetracyclin + cefdinir vs tetracyclin + minomycin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Tetracyclin + cefdinir vs tetracyclin + fosfomycin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Tetracyclin + minomycin vs tetracyclin + fosfomycin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

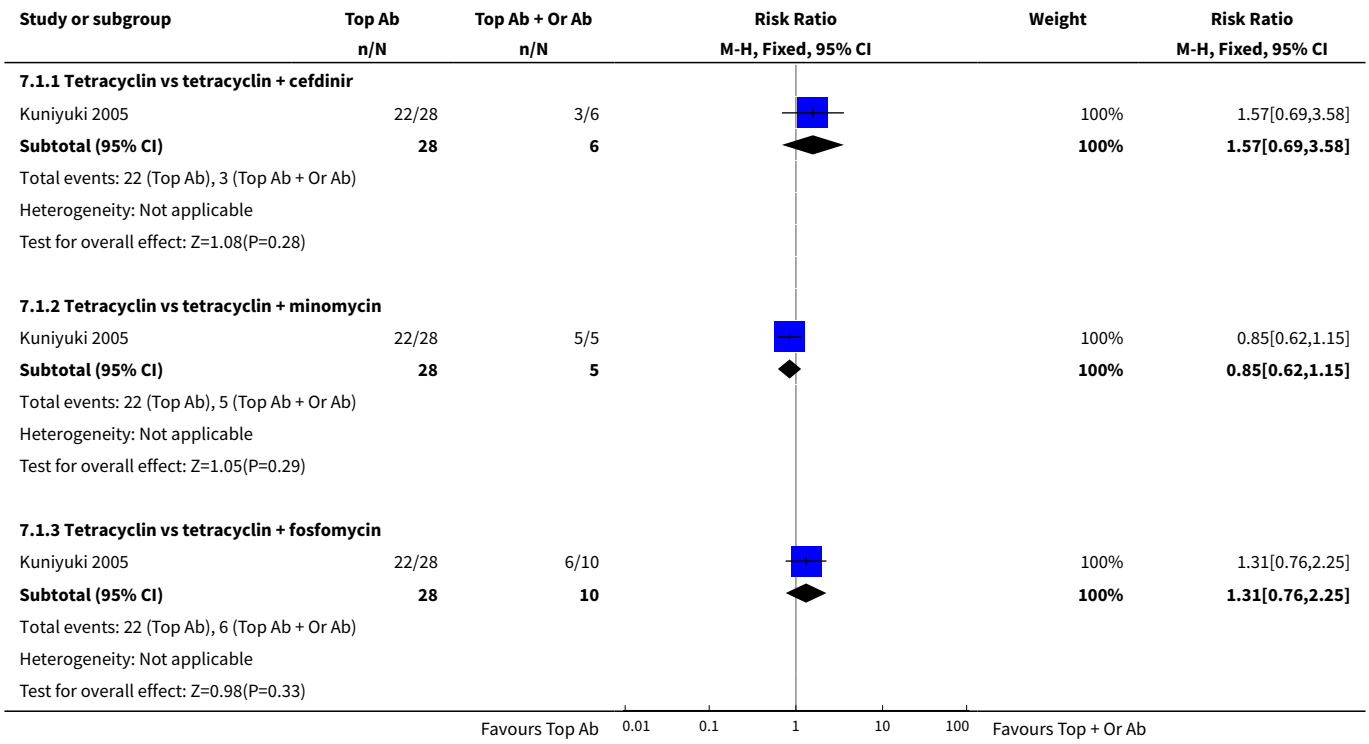
Analysis 6.1. Comparison 6 Non-bullous impetigo: topical (Top) antibiotic (Ab) + oral (Or) antibiotic (Ab) vs topical (Top) antibiotic (Ab) + oral (Or) antibiotic (Ab), Outcome 1 Cure.



Comparison 7. Non-bullous impetigo: topical (Top) antibiotic (Ab) vs topical (Top) antibiotic (Ab) + oral (Or) antibiotic (Ab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Tetracyclin vs tetracyclin + cefdinir	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.69, 3.58]
1.2 Tetracyclin vs tetracyclin + minomycin	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.62, 1.15]
1.3 Tetracyclin vs tetracyclin + fosfomycin	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.76, 2.25]

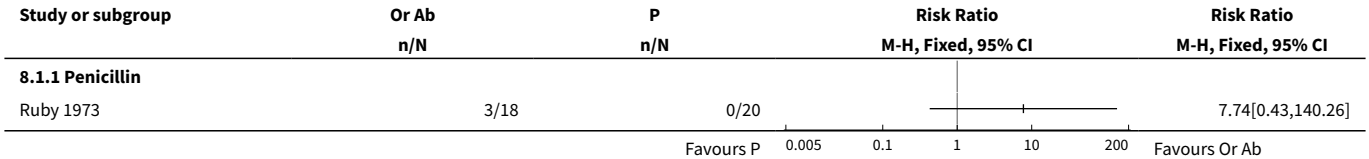
Analysis 7.1. Comparison 7 Non-bullous impetigo: topical (Top) antibiotic (Ab) vs topical (Top) antibiotic (Ab) + oral (Or) antibiotic (Ab), Outcome 1 Cure.



Comparison 8. Non-bullous impetigo: oral (Or) antibiotics (Ab) vs placebo (P)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Penicillin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 Non-bullous impetigo: oral (Or) antibiotics (Ab) vs placebo (P), Outcome 1 Cure/improvement.

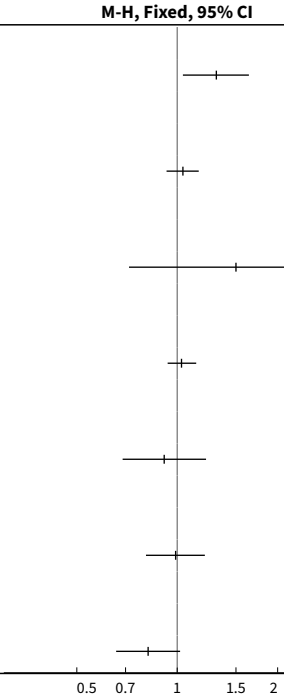


Comparison 9. Non-bullous impetigo: oral (Or) antibiotic (Ab) (cephalosporin) vs another oral (Or) antibiotic (Ab)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Cure/improvement	6		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Cephalexin vs penicillin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Cephalexin vs erythromycin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Cephalexin vs azithromycin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Cefaclor vs azithromycin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Cefaclor vs amoxicillin/clavulanic acid	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Cefadroxil vs penicillin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.7 Cefadroxil vs flucloxacillin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 Non-bullous impetigo: oral (Or) antibiotic (Ab) (cephalosporin) vs another oral (Or) antibiotic (Ab), Outcome 1 Cure/improvement.

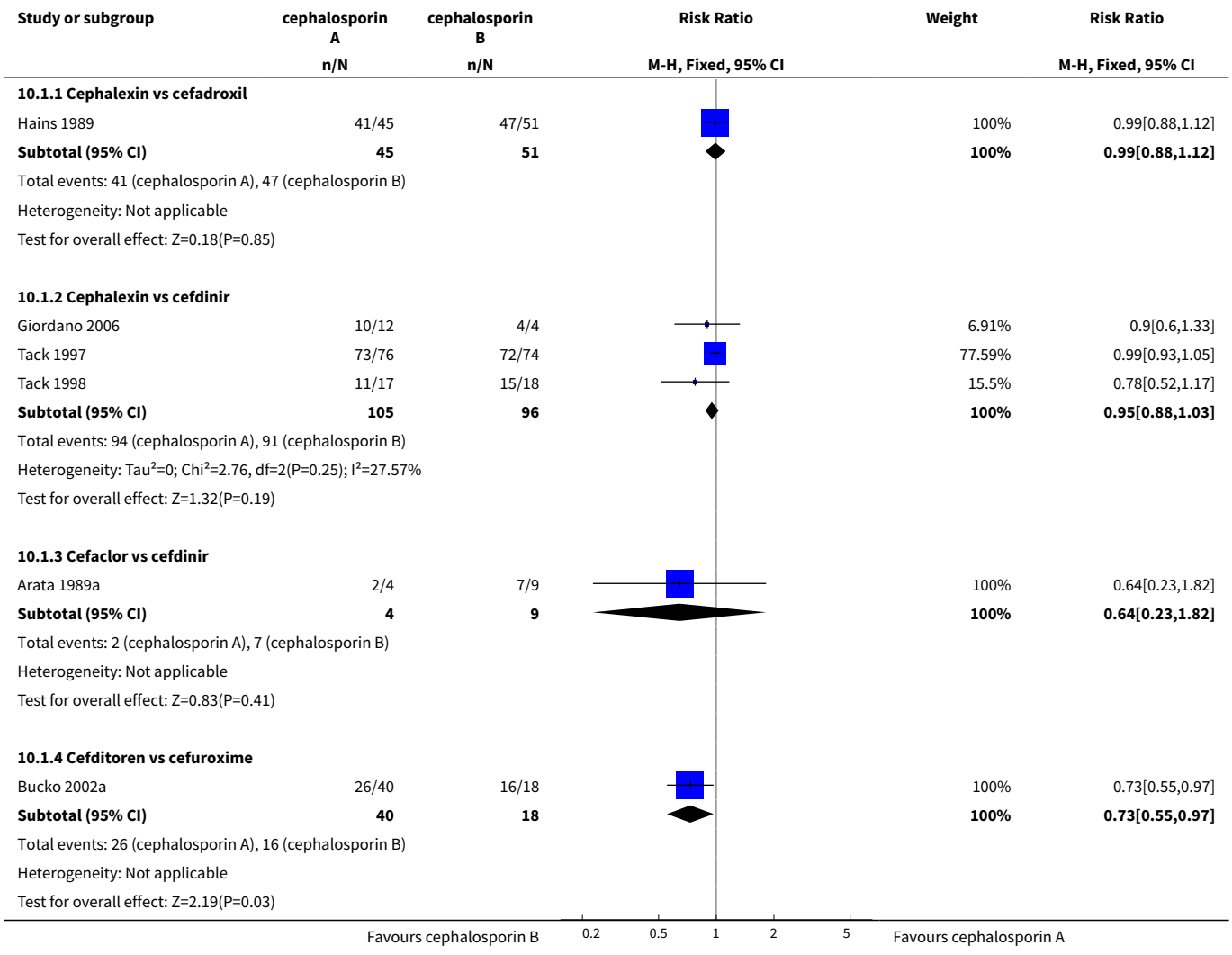
Study or subgroup	Or Ab n/N	Other Or Ab n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
9.1.1 Cephalexin vs penicillin				
Demidovich 1990	23/23	19/25		1.31[1.04,1.64]
9.1.2 Cephalexin vs erythromycin				
Demidovich 1990	23/23	24/25		1.04[0.93,1.16]
9.1.3 Cephalexin vs azithromycin				
Kiani 1991	6/8	5/10		1.5[0.72,3.14]
9.1.4 Cefaclor vs azithromycin				
Montero 1996	49/51	41/44		1.03[0.94,1.14]
9.1.5 Cefaclor vs amoxicillin/clavulanic acid				
Jaffe 1985	13/16	16/18		0.91[0.69,1.22]
9.1.6 Cefadroxil vs penicillin				
Ginsburg 1978	21/24	23/26		0.99[0.81,1.21]
9.1.7 Cefadroxil vs flucloxacillin				
Beitner 1996	25/33	25/27		0.82[0.66,1.02]

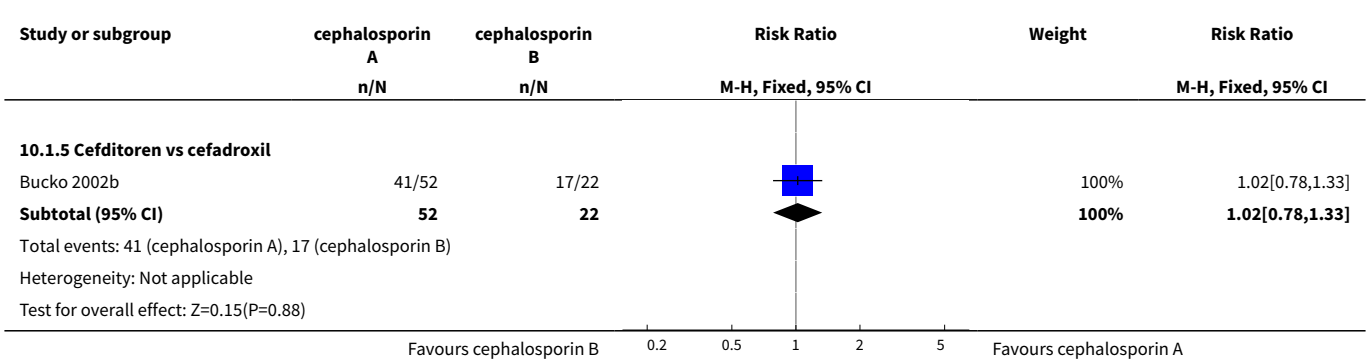


Comparison 10. Non-bullous impetigo: oral (Or) cephalosporin vs other oral (Or) cephalosporin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Cephalexin vs cefadroxil	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.88, 1.12]
1.2 Cephalexin vs cefdinir	3	201	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.88, 1.03]
1.3 Cefaclor vs cefdinir	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.23, 1.82]
1.4 Cefditoren vs cefuroxime	1	58	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.97]
1.5 Cefditoren vs cefadroxil	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.78, 1.33]

Analysis 10.1. Comparison 10 Non-bullous impetigo: oral (Or) cephalosporin vs other oral (Or) cephalosporin, Outcome 1 Cure/improvement.

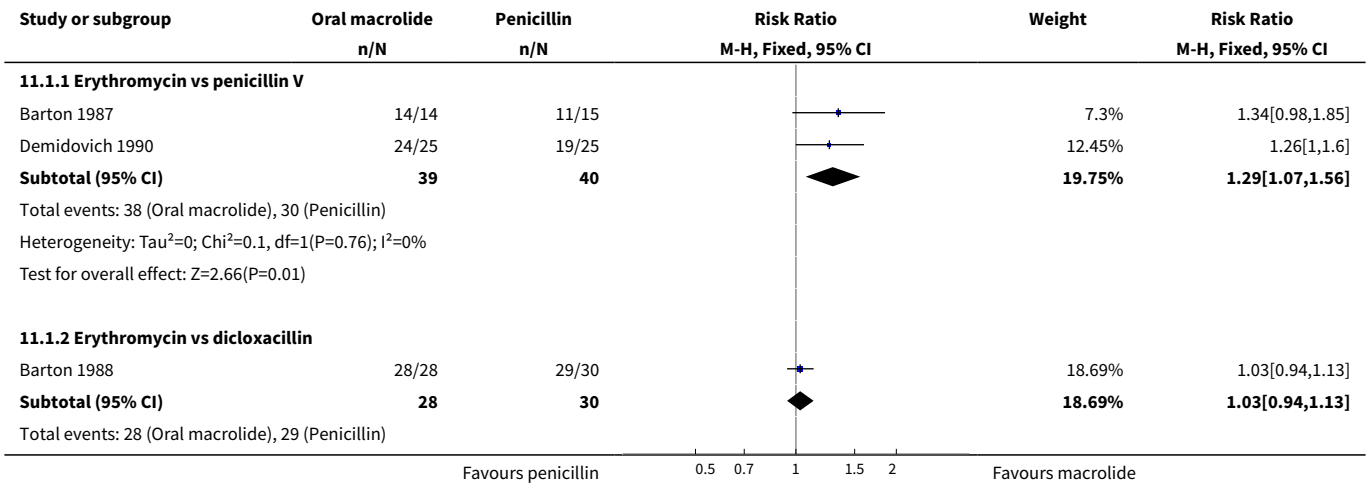


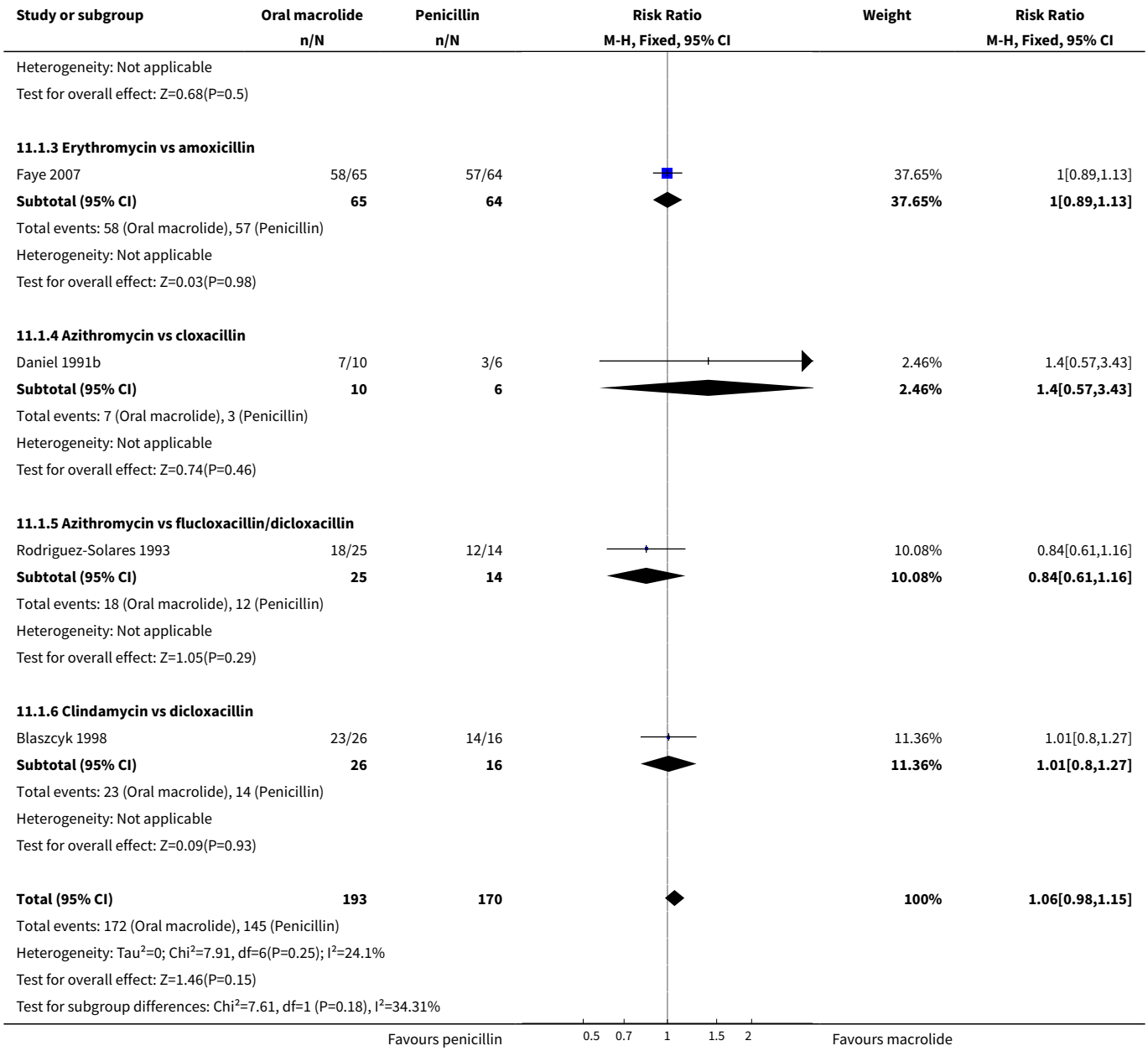


Comparison 11. Non-bullous impetigo: oral (Or) macrolide vs penicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	7	363	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.98, 1.15]
1.1 Erythromycin vs penicillin V	2	79	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.07, 1.56]
1.2 Erythromycin vs dicloxacillin	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.94, 1.13]
1.3 Erythromycin vs amoxicillin	1	129	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.89, 1.13]
1.4 Azithromycin vs cloxacillin	1	16	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.57, 3.43]
1.5 Azithromycin vs flucloxacillin/dicloxacillin	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.61, 1.16]
1.6 Clindamycin vs dicloxacillin	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.80, 1.27]

Analysis 11.1. Comparison 11 Non-bullous impetigo: oral (Or) macrolide vs penicillin, Outcome 1 Cure/improvement.

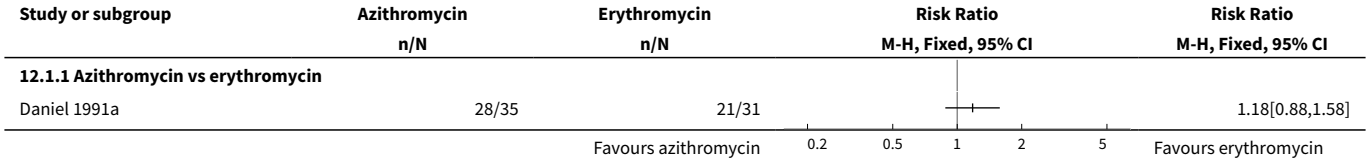




Comparison 12. Non-bullous impetigo: oral (Or) macrolide vs another oral (Or) macrolide

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Cure/improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Azithromycin vs erythromycin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

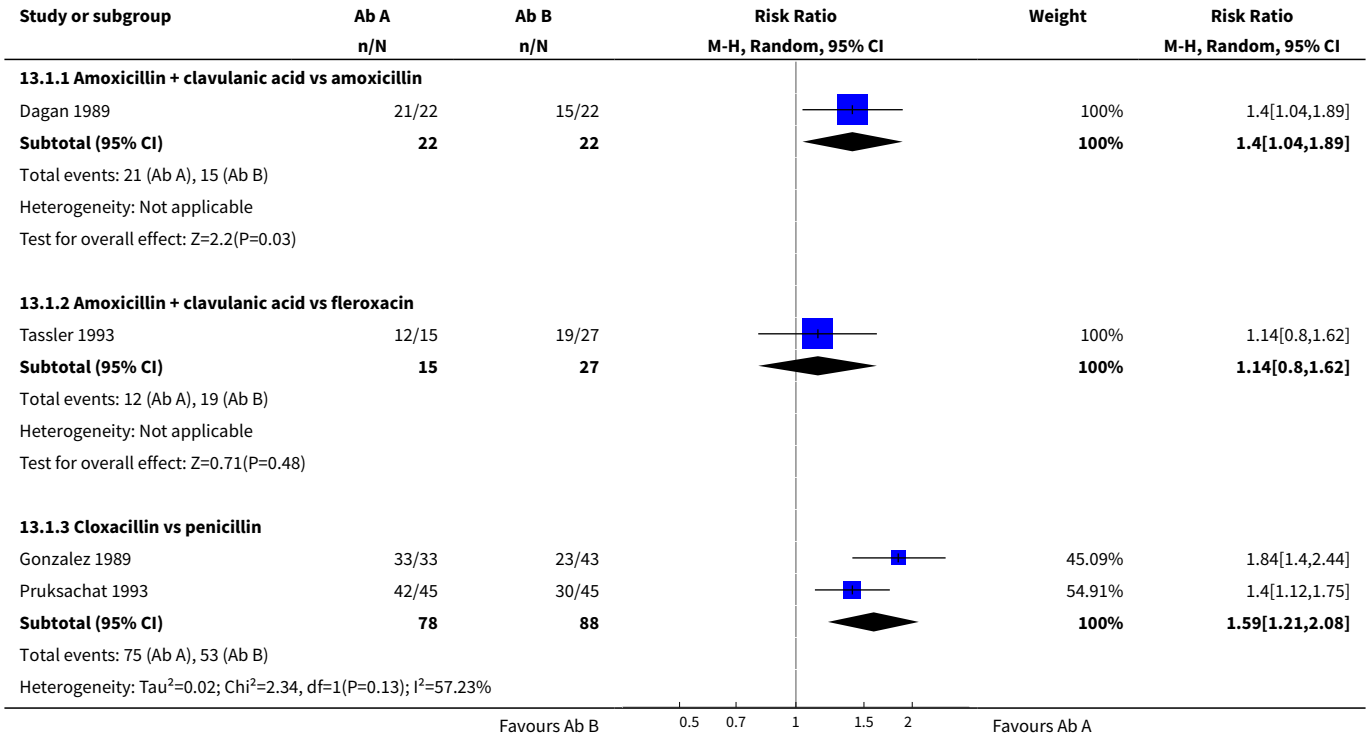
Analysis 12.1. Comparison 12 Non-bullous impetigo: oral (Or) macrolide vs another oral (Or) macrolide, Outcome 1 Cure/improvement.

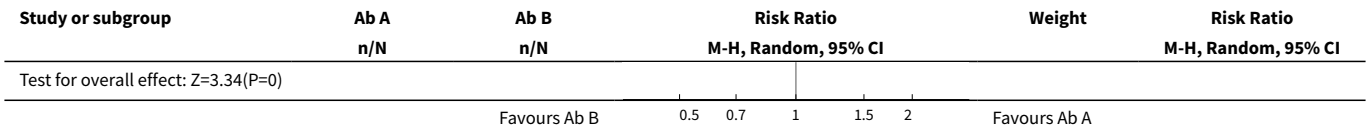


Comparison 13. Non-bullous impetigo: oral (Or) penicillin vs other oral (Or) antibiotic (Ab) (including penicillin)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Cure/improvement	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Amoxicillin + clavulanic acid vs amoxicillin	1	44	Risk Ratio (M-H, Random, 95% CI)	1.4 [1.04, 1.89]
1.2 Amoxicillin + clavulanic acid vs fleroxacin	1	42	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.80, 1.62]
1.3 Cloxacillin vs penicillin	2	166	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.21, 2.08]

Analysis 13.1. Comparison 13 Non-bullous impetigo: oral (Or) penicillin vs other oral (Or) antibiotic (Ab) (including penicillin), Outcome 1 Cure/improvement.

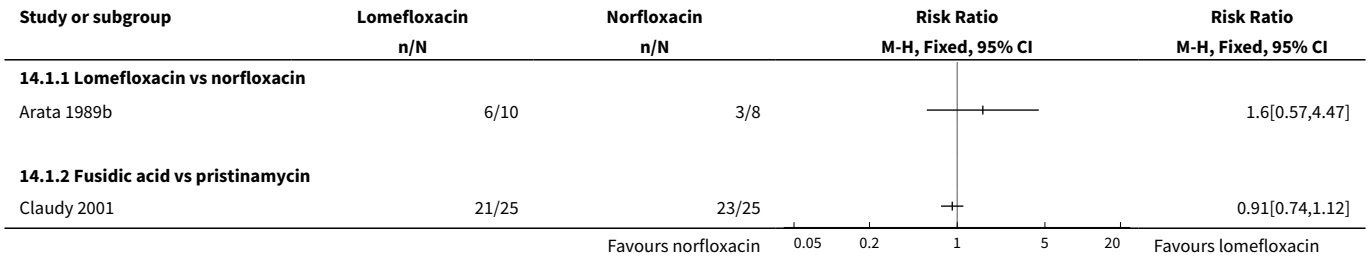




Comparison 14. Non-bullous impetigo: other comparisons of oral (Or) antibiotics (Ab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Lomefloxacin vs norfloxacin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Fusidic acid vs pristinamycin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

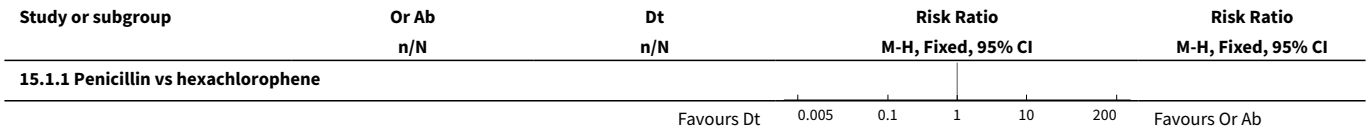
Analysis 14.1. Comparison 14 Non-bullous impetigo: other comparisons of oral (Or) antibiotics (Ab), Outcome 1 Cure/improvement.

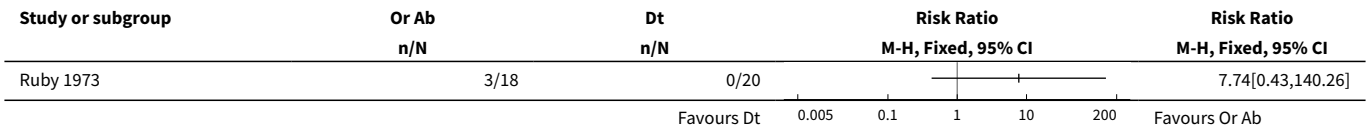


Comparison 15. Non-bullous impetigo: oral (Or) antibiotics (Ab) vs disinfecting treatments (Dt)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Penicillin vs hexachlorophene	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 15.1. Comparison 15 Non-bullous impetigo: oral (Or) antibiotics (Ab) vs disinfecting treatments (Dt), Outcome 1 Cure/improvement.

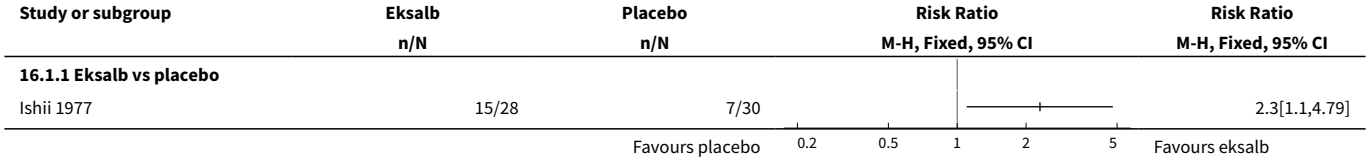




Comparison 16. Bullous impetigo: topical (Top) antimicrobial vs placebo (P)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cured/improved after 3 to 4 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Eksalb vs placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

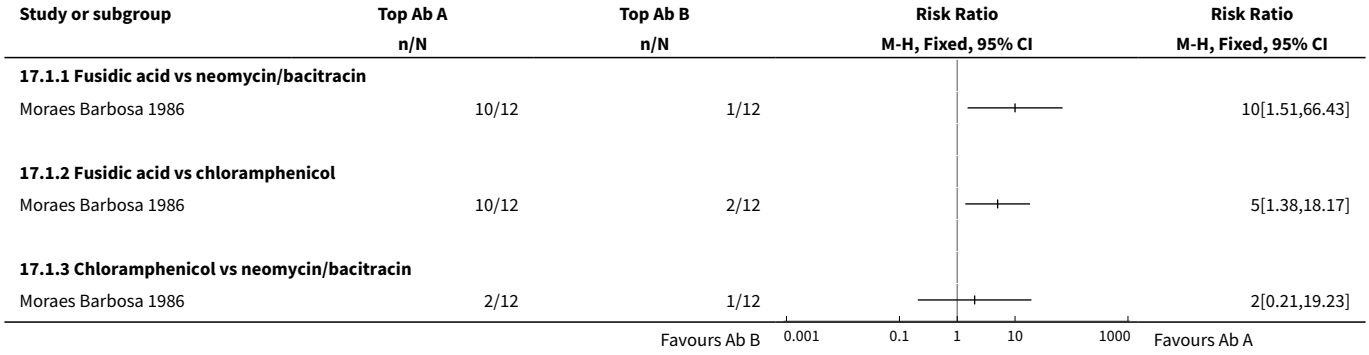
Analysis 16.1. Comparison 16 Bullous impetigo: topical (Top) antimicrobial vs placebo (P), Outcome 1 Cured/improved after 3 to 4 days.



Comparison 17. Bullous impetigo: topical (Top) antibiotic (Ab) vs another topical (Top) antibiotic (Ab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Fusidic acid vs neomycin/bacitracin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Fusidic acid vs chloramphenicol	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Chloramphenicol vs neomycin/bacitracin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

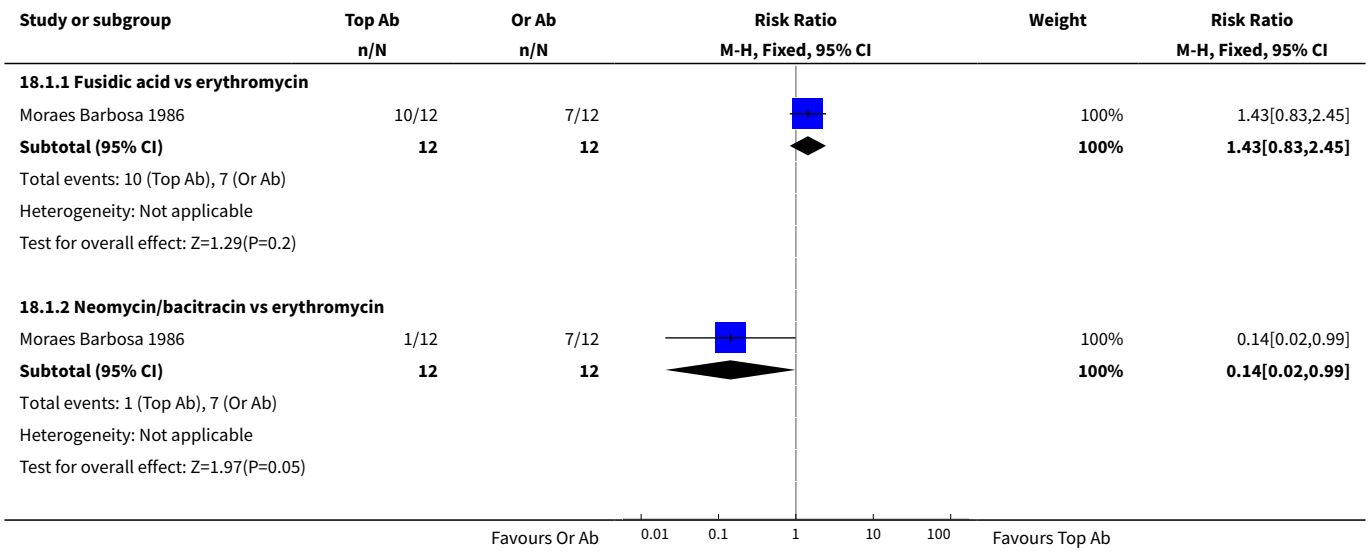
Analysis 17.1. Comparison 17 Bullous impetigo: topical (Top) antibiotic (Ab) vs another topical (Top) antibiotic (Ab), Outcome 1 Cure/improvement.

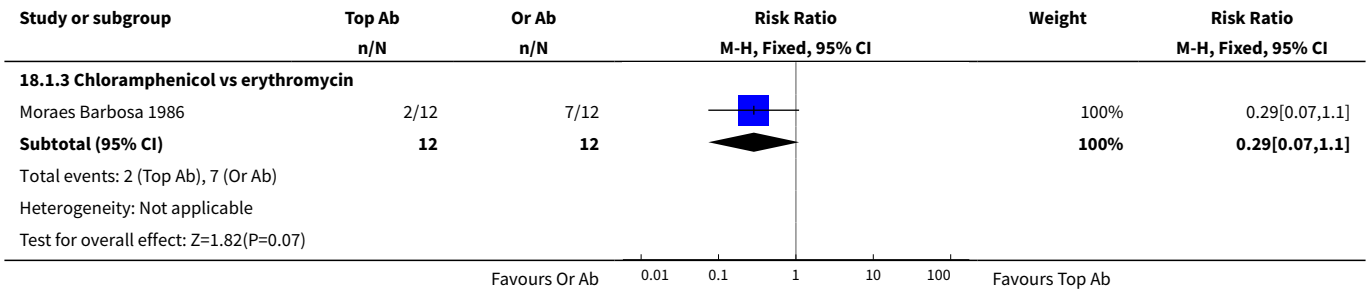


Comparison 18. Bullous impetigo: topical (Top) antibiotic (Ab) vs oral (Or) antibiotic (Ab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Fusidic acid vs erythromycin	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.83, 2.45]
1.2 Neomycin/bacitracin vs erythromycin	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 0.99]
1.3 Chloramphenicol vs erythromycin	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.07, 1.10]

Analysis 18.1. Comparison 18 Bullous impetigo: topical (Top) antibiotic (Ab) vs oral (Or) antibiotic (Ab), Outcome 1 Cure/improvement.

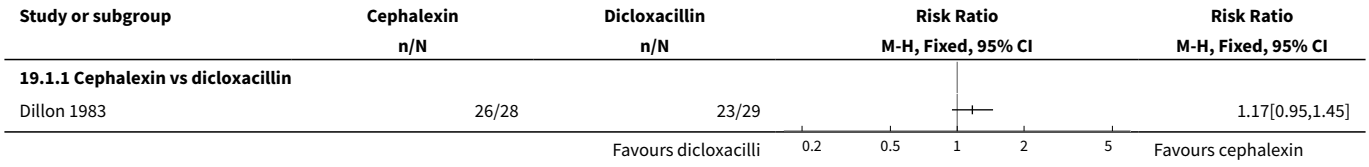




Comparison 19. Bullous impetigo: oral (Or) antibiotic (Ab) vs another oral (Or) antibiotic (Ab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Cephalexin vs dicloxacillin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 19.1. Comparison 19 Bullous impetigo: oral (Or) antibiotic (Ab) vs another oral (Or) antibiotic (Ab), Outcome 1 Cure/improvement.

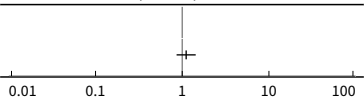


Comparison 20. Secondary impetigo: topical (Top) antibiotic (Ab) vs oral (Or) antibiotic (Ab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Mupirocin calcium vs cephalexin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 20.1. Comparison 20 Secondary impetigo: topical (Top) antibiotic (Ab) vs oral (Or) antibiotic (Ab), Outcome 1 Cure/improvement.

Study or subgroup	Favours cephalexin n/N	Favours mupirocin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
20.1.1 Mupirocin calcium vs cephalexin				
Rist 2002	52/82	44/77		1.11[0.86,1.43]

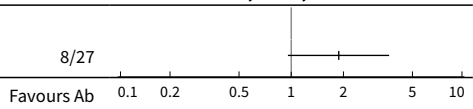


Comparison 21. Secondary impetigo: steroid (S) vs antibiotic (Ab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Betamethasone vs gentamycin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 21.1. Comparison 21 Secondary impetigo: steroid (S) vs antibiotic (Ab), Outcome 1 Cure/improvement.

Study or subgroup	S n/N	Ab n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
21.1.1 Betamethasone vs gentamycin				
Wachs 1976	15/27	8/27		1.88[0.96,3.67]

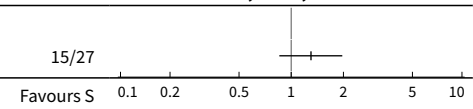


Comparison 22. Secondary impetigo: steroid (S) + antibiotic (Ab) vs steroid (S)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Betamethasone + gentamycin vs betamethasone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 22.1. Comparison 22 Secondary impetigo: steroid (S) + antibiotic (Ab) vs steroid (S), Outcome 1 Cure/improvement.

Study or subgroup	S + Ab n/N	S n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
22.1.1 Betamethasone + gentamycin vs betamethasone				
Wachs 1976	18/25	15/27		1.3[0.85,1.97]



Comparison 23. Secondary impetigo: steroid (S) + antibiotic (Ab) vs antibiotic (Ab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Betamethasone + gentamycin vs gentamycin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 23.1. Comparison 23 Secondary impetigo: steroid (S) + antibiotic (Ab) vs antibiotic (Ab), Outcome 1 Cure/improvement.

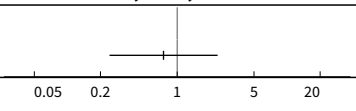
Study or subgroup	S + Ab n/N	Ab n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
23.1.1 Betamethasone + gentamycin vs gentamycin				
Wachs 1976	18/25	8/27		2.43[1.29,4.57]

Comparison 24. Secondary impetigo: oral (Or) antibiotic (Ab) vs another oral (Or) antibiotic (Ab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure/improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Cephalexin vs enoxacin	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 24.1. Comparison 24 Secondary impetigo: oral (Or) antibiotic (Ab) vs another oral (Or) antibiotic (Ab), Outcome 1 Cure/improvement.

Study or subgroup	Cephalexin n/N	Enoxacin n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
24.1.1 Cephalexin vs enoxacin				
Fujita 1984	2/4	4/6		0.75[0.24,2.33]



ADDITIONAL TABLES

Table 1. Adverse events

Study	Adverse events: nature and number or percentage by treatment group

Table 1. Adverse events *(Continued)*

Arata 1989a; Arata 1989b	mainly gastrointestinal: cefdinir 9/142, cefaclor 4/145
Arredondo 1987	mupirocin: nil reported dicloxacillin: abdominal pain 1/ 31, vomiting 2/31
Barton 1987	not reported
Barton 1988	abdominal pain: erythromycin 1/ 49, dicloxacillin 1/51 vomiting + rash: dicloxacillin 1/51
Barton 1989	gastrointestinal: erythromycin 8/48, mupirocin 4/49
Bass 1997	not reported
Beitner 1996	diarrhoea: cefadroxil 14/327, flucloxacillin 87/324 (all participants) severe (stomach ache/rash/fever/vomiting): cefadroxil 14/327, flucloxacillin 2/234 (all participants)
Blaszcyk 1998	mainly gastro-intestinal (half of which were considered treatment-related): clindamycin 150 mg (19%), clindamycin 300 mg (17%), dicloxacillin 10% (all participants)
Britton 1990	minor gastrointestinal: 11 total, equally divided
Bucko 2002a; Bucko 2002b	unclear and not specified for impetigo participants
Christensen 1994	led to withdrawal: skin irritation 1, burning 1, blistering 1 (all fusidic acid - hydrogen peroxide: 0) mild SE: fusidic acid 9, hydrogen peroxide 13
Ciftci 2002	burning, stinging, itching: 1 in each group rash: 1 in terbinafine group
Claudy 2001	upper gastrointestinal: fusidic acid 6.8% vs pristinamycin 11.6% lower gastrointestinal: 2.5% vs 16.7% hypersensibility: 1.9% vs 5.8%
Dagan 1989	vomiting: amoxicillin 1, amoxicillin and clavulanic acid (augmentin) 0 diarrhoea: amoxicillin 1, amoxicillin and clavulanic acid (augmentin) 0
Dagan 1992	gastrointestinal: erythromycin 11/47, mupirocin 4/51
Daniel 1991a; Daniel 1991b	no subgroup data
Demidovich 1990	nil reported
Dillon 1983	not reported
Dux 1986	pruritus: mupirocin 1/78 nausea and abdominal pain: erythromycin 1/50, cloxacillin 0/20 (all participants)
Eells 1986	not reported
Esterly 1991	mupirocin: nil reported

Table 1. Adverse events *(Continued)*

	erythromycin: stomach pain and nausea 1/20, vomiting and irritability 1/20, hysterical attacks 1/20
Farah 1967	not reported
Faye 2007	diarrhoea: amoxicillin 2/64 vs erythromycin 11/65
Fujita 1984	mainly gastrointestinal: enoxacin 11/113, cephalexin 4/110 (all participants)
Gilbert 1989	nil reported
Ginsburg 1978	1 child removed from cefadroxil group because of vomiting; no other SE reported
Giordano 2006	diarrhoea: cefdinir 10% vs cephalexin 4% nausea: cefdinir 3% vs cephalexin 6% vaginal mycose of females: cefdinir 3% vs cephalexin 6%
Goldfarb 1988	mild diarrhoea: amupirocin 0/30, erythromycin 5/30
Gonzalez 1989	not reported
Gould 1984	not reported
Gratton 1987	mostly gastrointestinal: erythromycin 8/29 mupirocin: nil reported
Hains 1989	nil reported
Ishii 1977	nil reported
Jaffe 1985	mild diarrhoea: Augmentin® 2/18, cefaclor 5/16 (all participants)
Jaffe 1986	mild staining: hydrocortisone + potassium hydroxyquinoline sulphate cream 2/24, 1% hydrocortisone + 2% miconazole nitrate cream 0/24
Kennedy 1985	nil reported
Kiani 1991	mainly gastrointestinal: azithromycin 30/182, cephalexin: 20/184 Withdrawn: azithromycin 5 (4 gastrointestinal; 1 dizziness and somnolence), cephalexin 1(euphoria) (all participants)
Koning 2003	mainly pain and burning due to povidone iodine: fusidic acid 7/76, placebo 19/80
Koning 2008	any: retapamulin 15/139 vs placebo 2/71 application site pruritis: 9 vs 1
Koranyi 1976	mild abdominal cramps: erythromycin 2/15, bacitracin 0/15
Kuniyuki 2005	not reported
McLinn 1988	gastrointestinal: mupirocin 0/30, erythromycin 6/30
Mertz 1989	nil reported

Table 1. Adverse events *(Continued)*

Montero 1996	mild skin side-effects: azythromycin 3/100, cefaclor 2/100
Moraes Barbosa 1986	not reported
Morley 1988	all local skin reactions: sodium fusidate 2/191, mupirocin 12/163 (all participants)
Nolting 1988	mild burning: sulconazole 0/32, miconazole 1/34
Oranje 2007	local irritation: retapamulin 6/346 vs sodium fusidate 0/173
Pruksachat 1993	not reported
Rice 1992	stomach ache/diarrhoea/vomiting/itching/burning (%): erythromycin 24/10/7/5/0, mupirocin 2/2/0/12/10
Rist 2002	diarrhoea: mupirocin 2/82 vs cephalexin 3/77
Rodriguez-Solares 1993	gastrointestinal: azithromycin 2/25, dicloxacillin/flucloxacillin 2/14
Rojas 1985	nausea/vomiting: mupirocin 0/52, vehicle 1/52
Ruby 1973	not reported
Sutton 1992	local: fusidic acid 2/104, mupirocin 4/97
Tack 1997	mainly gastrointestinal: cefdinir 16%, cephalexin 11% (all participants)
Tack 1998	no subgroup data was available; it included only participants that had pathogens susceptible to both study drugs
Tamayo 1991	nil reported
Tassler 1993	mainly gastrointestinal: fleroxacin 17%, amoxicillin/clavunalate 21% (all participants)
Vainer 1986	total 3% skin rash: fusidic acid 1/43 burning and itching: tetracycline/polymyxin B ointment and neomycin/bacitracin ointment both 1/44 and 1/41 respectively
Wachs 1976	not reported
Wainscott 1985	nil reported
Welsh 1987	nil reported
White 1989	minor itching or burning: mupirocin 6/263, fusidic acid 2/127 (all participants)
Wilkinson 1988	rash: mupirocin 0/24, neomycin 1/26 (all participants)

Table 2. Declared sponsorship or funding

Study	Sponsor (product)

Table 2. Declared sponsorship or funding *(Continued)*

Barton 1987	Fleur de Lis Foundation
Barton 1988	Warner-Lambert Corporation
Barton 1989	Warner- Lambert Corporation
Beitner 1996	Bristol-Myers Squibb (cefadroxil)
Blaszcyk 1998	Pharmacia & Upjohn Asia (clindamycin)
Britton 1990	US Navy Bureau of Medicine and Surgery Clinical Investigation Program
Bucko 2002a, Bucko 2002b	TAF Pharmaceutical Products (cefditoren)
Daniel 1991a; Daniel 1991b	Pfizer Central Research (azithromycin)
Dillon 1983	Eli Lilly Research (cephalexin)
Giordano 2006	Abott Laboratories (cefdinir)
Goldfarb 1988	Beecham Laboratories (mupirocin)
Hains 1989	Bristol-Myers Squibb (cefadroxil)
Jaffe 1985	Beecham Laboratories (amoxicillin+clavulanic acid)
Koning 2003	Dutch College of General Practitioners
Koning 2008	GlaxoSmithKline (retapamulin)
Mertz 1989	Beecham Laboratories (mupirocin)
Oranje 2007	GlaxoSmithKline (retapamulin)
Rist 2002	GlaxoSmithKline (mupirocin)
Sutton 1992	Leo Laboratories (fusidic acid)
Tack 1997	Parke-Davis pharmaceutical research (cefdinir)
Tack 1998	Parke-Davis pharmaceutical research (cefdinir)
Wainscott 1985	Beecham Pharmaceuticals (mupirocin)
White 1989	Beecham Pharmaceuticals (mupirocin)

APPENDICES

Appendix 1. CENTRAL search strategy

#1(impetig* or pyoderma):ti
#2MeSH descriptor Impetigo explode all trees in MeSH products
#3(#1 OR #2)
#4SR-SKIN in All Fields in all products

#5(#3 AND NOT #4)

Appendix 2. MEDLINE (OVID) search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animals not (human and animals)).sh.
10. 8 not 9
11. exp Staphylococcal Infections/ or stapylococcal skin infections.mp.
12. impetigo.mp. or exp Impetigo/
13. exp Pyoderma/ or pyoderma.mp.
14. 11 or 13 or 12
15. 10 and 14

Appendix 3. EMBASE (OVID) search strategy

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. (assign$ or allocat$).mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. impetigo.mp. or exp IMPETIGO/
15. exp PYODERMA/ or pyoderma.mp.
16. exp Staphylococcus Aureus/ or stapylococcus aureus.mp.
17. 16 or 15 or 14
18. 13 and 17

Appendix 4. LILACS search strategy

((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control$ or tw aleat$ or tw random$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Palavras] and (impetigo or pyoderma or piodermia or piodermitis or (staphyloccus aureus) or estafilococo) [Palavras]

WHAT'S NEW

Date	Event	Description
9 June 2015	Amended	Author information (affiliation) updated

HISTORY

Protocol first published: Issue 4, 2001
Review first published: Issue 2, 2004

Date	Event	Description
7 March 2012	Amended	The lead author's contact details have been updated.
8 November 2011	New citation required but conclusions have not changed	A substantial amount of new information has been added in the form of 12 newly included studies.
8 November 2011	New search has been performed	New search for studies
29 July 2011	Feedback has been incorporated	In response to peer reviewers' comments, the following major changes were implemented: (1) removed sumscore for risk of bias items; (2) dropped intention to treat analysis as separate risk of bias item; (3) provided more precise information on subjective assessment of symptoms; (4) made a separate table for adverse events.
4 August 2010	Amended	When finalizing the update, new searches were run (2009-July 2010), resulting in the addition of eight papers to the list of Studies awaiting assessment.
23 February 2009	New citation required and conclusions have changed	New search (2002-2008), 12 new trials found, one trial previously included discarded. Tables with outcomes of methodological assessments replaced by 'Risk of bias' tables. New author added.
3 October 2008	Amended	Converted to new review format.
2 September 2004	New search has been performed	Minor update
4 January 2003	Amended	New studies found but not yet included or excluded
27 November 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Conceiving the review - SK, JCvdW, and LvSS
Designing the review - SK, JCvdW, LvSS, CCB, and AM
Co-ordinating the review - SK and JCvdW
Data collection for the review - SK, JCvdW, and RvdS
Developing the search strategy - JCvdW
Undertaking searches - JCvdW, SK, and RvdS
Screening search results - JCvdW, SK, and RvdS
Organising retrieval of papers - JCvdW, SK, and RvdS
Screening retrieved papers against inclusion criteria - LvSS, SK, and RvdS
Appraising quality of papers - JCvdW, AV, and RvdS
Abstracting data from papers - CCB, AM, RvdS, and JCvdW
Writing to trial authors of papers for additional information - SK, RvdS, and JCvdW
Obtaining and screening data on unpublished studies - JCvdW, SK, and RvdS
Data management for the review - SK, RvdS, and JCvdW
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Analysis of data - SK, RvdS, and JCvdW
Interpretation of data - all authors

Providing a methodological perspective - JCvdW
Providing a clinical perspective - SK and CCB
Providing a policy perspective - SK and CCB
Writing the review - SK, RvdS, and JCvdW
Providing general advice on the review - all authors
Securing funding for the review - JCvdW
Performing previous work that was the foundation of current study - LvSS, JCvdW, and SK

DECLARATIONS OF INTEREST

Three authors of this review are authors of one included trial (Sander Koning, Lisette WA van Suijlekom-Smit, Johannes C van der Wouden; Koning 2003).

Sander Koning and Johannes C van der Wouden were also involved in a second trial (Koning 2008), which was initiated by the manufacturer of the drug. As employees of Erasmus MC, Rotterdam, Johannes C van der Wouden and Sander Koning received research funding from GlaxoSmithKline for participating in a study comparing retapamulin to placebo in participants with impetigo. The funding was used to pay staff involved in field work. They were also involved in publishing the results. The study was included in the update of this review.

SOURCES OF SUPPORT

Internal sources

- Department of General Practice, Erasmus MC - University Medical Center Rotterdam, Netherlands.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In case of studies assessing cure at more than one point in time, the protocol did not specify what time point to select for data extraction. From the start of the review, we chose the assessment that was closest to one week from the start of treatment.

For this update, the scoring of methodological quality was changed into the newly recommended 'Risk of bias' table (Higgins 2008).We also used risk ratio as recommended by the Cochrane Skin Group.

NOTES

Sponsored research

Industry sponsorship or organisation of the trial was declared to be present in 20 trials (29%): 5 mupirocin studies (Goldfarb 1988; Mertz 1989; Rist 2002; Wainscott 1985; White 1989), 2 with cefdinir (Tack 1997; Tack 1998), 2 with cefadroxil (Beitner 1996; Hains 1989), 2 with azithromycin (Daniel 1991a; Daniel 1991b), 2 with cefditoren (Bucko 2002a; Bucko 2002b); 2 with retapamulin (Koning 2008; Oranje 2007); 1 of amoxicillin plus clavulanic acid (Jaffe 1985), cefalexin (Dillon 1983; Giordano 2006), clindamycin (Blaszcyk 1998), and fusidic acid (Sutton 1992). Five trials (9%) were supported by other organisations. In the remaining 48 (67%) trials, no statement of sponsorship or funding was made (see Table 2 '*Declared sponsorship or funding*').

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Administration, Topical; Anti-Bacterial Agents [administration & dosage] [*therapeutic use]; Erythromycin [administration & dosage] [therapeutic use]; Fusidic Acid [administration & dosage] [therapeutic use]; Impetigo [*drug therapy]; Mupirocin [administration & dosage] [therapeutic use]; Penicillins [administration & dosage] [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans